The University of North Carolina and the American Chemistry Council Collaborated to Organize a Workshop

FORMALEHYDE SCIENCE INVITED EXPERTS WORKSHOP UNDERSTANDING POTENTIAL HUMAN HEALTH CANCER RISK – FROM DATA INTEGRATION TO RISK EVALUATION

October 10 – 11, 2017

Location: UNC Friday Center, 100 Friday Center Drive, Chapel Hill, NC 27599

Co-Chairs: Drs. James Swenberg and Kenneth Mundt



Points for the discussions today:

- Background about formaldehyde
- The current risk assessment landscape
- The meeting itself goal, invitees, session structure, topics
- Overview of some of the conclusions/recommendations from the meeting
- Recommendations for integrating data streams into a formaldehyde risk evaluation



Some Background about Formaldehyde At concentrations above 6 ppm in rats, where there is clear cytotoxicity and cell replication, it causes nasal cancer in rats. One of the most extensively studied chemical carcinogens Present in all cells at an appreciable level - tenths of mmoles/liter Estimated background exhaled concentrations of several ppb Endogenous formaldehyde-DNA reaction products have a high background Inconsistent epidemiology in occupational cohorts Risk assessments across the world are highly divergent



A View of the Risk Assessment Landscape POPULATION APPROACH RISK LEVEL ORGANIZATION Basis of Decision EU/ECHA No convincing evidence of General Qualitative but not low-Causes tumors above a threshold concentration a carcinogenic effect at dose linear by mechanisms that are initiated by the distant sites cytotoxic effects but ...data does not allow firm conclusion on a threshold-mode of action" 2.3 x 10⁻¹⁰ at 1 ppb Threshold Carcinogen **Health Canada** General Carcinogenic hazard to humans "...under **DSL** Low priority conditions that induce cytotoxicity and sustained substance regenerative cell proliferation." Occupational Workers Threshold Carcinogen Exposure standards: Varied: from MAK - Cancer classification 4: non-Standards from TWAs with STELs genotoxic; cell proliferation important to MoA to various bodies 0.1 ppm ACGIH; 0.016 pp ACGIH's "cancer classification A1: confirmed In the US and EU NIOSH; NIOSH; 3ppm human carcinogen " MAK and SCOEL NTP Report on Sufficient evidence in humans for nasal tumors Qualitative Known human carcinogen Carcinogens and myeloid leukemia (2011) Qualitative IARC Known human carcinogen Sufficient evidence in humans for tumors at both Monographs 10F (2010) sites 1 x 10 ⁻⁴ at 1 ppb IRIS General Low dose linear For NPC, mutagenic MoA operating in conjunction (2010) with key event of formaldehyde cytotoxicityinduced cell proliferation, sufficient evidence of causal association for NPC and LHP cancer in humans



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With ongoing work on a new IRIS assessment, it was considered an opportune time to bring together highly-regarded, subject matter experts and discuss how diverse data streams could be brought together to conduct an up-to-date risk evaluation Formaldehyde Science Invited Experts Workshop Attendee List

Name	Affiliation	Emai		
Bruce Rodan	Environmental Protection Agency	Roden bruce @Epapov		
Chap Thompson	ToxStrategies, Inc.	ethennson@toxshrategien.com		
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Enri co Pira	University of Turin	earine pins@earite if		
Erin Dickison	American Chemistry Council	Brin, Diskison (bunterican chanistry cont		
Gary Marsh	University of Pittsburg	somá-fojit sá		
Harvey Checkoway	University of California San Diego	tebaskovaviĝisoskiedu		
Harvey Clewell	ScitoVation/Ramboll Environ	noo oois votie Gilberala		
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Hermann Bolt	Independent Consultant	an beligae coa		
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Jim Swenberg	University of North Carolina	sweether/berrail sac sets		
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Paol o Boffetta	Icahn School of Medicine at Mount Sinai	ones e be fieling) cressu a du		
Raj Sharma	Georgia-Pacific	ार्व .संप्रतार अधि शराबद .घ्यारा		
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Rory Conolly	Environmental Protection Agency	Consily rosy@Fpa gev		
Sam Cohen	University of Nebraska Medical Center	mohan@anna.edu		
Stewart Hoim	American Forest & Paper Association	Slevet BrimSafandps.org		
Sue MacMillan	Oregon Department of Environmental Quality	y scena meand natistale acus		
Tom Starr	TBS Associates	Defentiĝistos Luncució:		

Four regulatory scientist – Bruce Rodan, Kris Thayer, Iris Camacho and Sue McMillan – and one EPA scientist from NHEEL – Rory Conolly.



FORMALEHYDE SCIENCE INVITED EXPERTS WORKSHOP UNDERSTANDING POTENTIAL HUMAN HEALTH CANCER RISK - FROM DATA INTEGRATION TO RISK EVALUATION October 10 - 11, 2017 Location: UNC Friday Center, 100 Friday Center Drive, Chappel Hill, NC 27599 Co-Chairs: Drs. James Swenberg and Kenneth Mundt TUESDAY, OCTOBER 16, 2017 The loss of the TUESDAY, OCTOBER 10, 2017 Discussion - Key Views by Farticipants on Charge Questions Charge Question #7 Discussion (30 minutes) Charge Question #8 Discussion (36 minutes) Open Discussion (15 minutes) 4:15рт — 5:30рт WEBNESDAY, OCHORER 11, 2017 WEDSTSIAN, OF OBER 11, 2017 Time Bross Som Stream REFERENCE (TWF Fields Center. More Veryland and Photosy Are) REMINISTRY OF STREAM FOR STREAM AND A RESERVED FROM THE CHARLES AND A RESIDENCE OF THE CHARLES AND A RESIDENCE OF THE CHARLES AND A RESIDENCE OF THE STREAM AND A Overview of State-of-the-Science Approaches for Data Integration - Kimberly Wisie (15 cainsies) Recap of Day 1 Discussion: Identified Data Gaps and Uncertainties -Information Needs for a Formaldeliyde Risk Evaluation Met Andersea (15 9.15-9:30am Information Needs for at Pennaldebride Relation Let Canamitae measures. Discretion—Key Views by Participants on Charge Guestions Discretion—Key Views by Participants on Charge Guestions Charge Question #10 Doctrosons (30 minutes) Charge Question #10 Doctrosons (30 minutes) Charge Question #11 Doctrosons (30 minutes) Charge Question #12 Discretions (30 minutes) Charge Question #13 Doctrosons (30 minutes) Open Datescons (15 minutes) Views (30 minutes) Workship Wings and Vest Steps DISCRETION #13 DOCTROSONS (30 minutes) | Copps | Live Carlos | Live Carlos | Copps | Copps | Copps | Live Carlos | Copps | Live Carlos | Li 9:50am - 11:45am 11:45ma - 12:00pra



SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY

- 1. Does the available scientific evidence support a specific MOA and causal association
 - c. What mechanistic evidence is available to support the proposed modes of action

framework discussed for NPC Whit are the uncertainties?

Suggested Discussants for Charge Question: Mel Andrew. Hommon Bolt, Harvey Clewell, Rocy Condly, Gary Masch

- 2. What are the key animal data for characterizing the shape of the dose-response curve for formaldehyde-induced ussal minors? What are the key epidemiological studies for formaldehyde-induced ussal tumors and how would you recencile differences between
 - If a causal association can be established for human, what exposure metrics are associated with evidence of carcinogenicity? Is these evidence of a threshold for NPC in humans?

Suggested Discussants for Charge Question: Mel Andersen, Herman Bob, Harvey Clewell. Rosy Cosolly. Peter Gelbke, Helmut Greim. Gary Marsh

- What quantitative methods (e.g., linear and non—linear low dose extrapolation, threshold, PBPK modeling for dose response assessment) would best characterize the potential for NPC risk in humans?

 Are there uncertainties wife any of these quantitative methods that suggest this

type of modeling shools not be applied? Suggested Discussants for Charge Question: Harvey Clewell, Rocy Conolly, Robinia Gentry, Tona Start

SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY

- 4. What does the totality of the animal and epidemiology evidence tell us about the potential for a crusal association with LEP and what conclusions can be drawn:

 What role does endogenous production play in drawing conclusions regarding
 - LHP?
 - $_{\odot}$. Do the available data support a specific mode of action for hematopoietic cancers?

Singgested Discussants for Charge Question: Paolo Bofetta, Harvey Checkoway, David Coggon, Sam Cohen, Robinson Gentry, Joseph Haney, Erico Pina, Jim Swenberg, Michael Thirman, Chad Thompson

- 5. What mechanishe data are critical to understanding a causal association between formaldeleyde exposure and specific hematopoietic cancers? Suggested Discussants for Charge Question: Rosy Conolly, Tom Start, Jun Swenberg, Michael Thuman
- Do epidemiology studies provide useful dose response data for LRP?
 Suggested Discussants for Charge Question: Rosy Conolly, Youa Start, Jun Swenberg Michael Thirmso
- 7. What methods for assessing causality and evidence integration are best applied to the svalable data for LHP cancer for conducting a hazard assessment (e.g. Bradford Hdl cuteria, biological systems approach, hypothesis based weight of evidence framework systematic review, combination of approaches?)

Suggested Discussants for Charge Question: Mei Andresen, Paulo Boffetta, Harvey Checkoway, David Coggon, Ken Mundt, Enrico Pirs, Kris Thayer

8. What uncertainties are important for consideration when integrating the available evidence? Suggested Discussants for Charge Question; Mel Anderson, Jan Bus, Harvey Clewell, Sam Cohen, Robinsu Gentry, Tom Starr



SESSION 3-FORMALDEHYDE-DATA RICH CHEMICAL RIPE FOR RISK EVALUATION?

- Want should be considered as the problem formulation and questions to be addressed when conducting a formulability of risk evaluation?
- 10. What are the best available approaches to contact a robust evaluation of formaldehyde carciangenic potential?
- 11. How can the approaches used to evaluate and integrate scientific evidence inform the risk accomment?
 - What aspects of the Biological Systems Approach can be used to integrate the formaldehyde data?
 - How can hypothesis based weight of evidence approach be to integrate the data oftenns for determination of causality?
- 12. What needs to be added or changed in the draft IPCS Mode of Action Framework musul carcinogenicity?
- 13. What is the comparative weight of evidence for each hypothesized mode of action for usual cardinogenicity?

Suggested Discussants for All Charge Questions - All Participants

Today, we want to convey a sense of the discussions, conclusions and recommendations from the group for the path forward

- Dr. Swenberg formaldehyde DNA-reaction products in various tissues from rodents and monkeys and their implications for responses to formaldehyde beyond the front of the nose.
- II. Dr. Mundt key recent epidemiological evaluations related to NPC, AML and Mode of Action
- III. Dr. Andersen recommendation for integrating the rodent and human studies into a more quantitative risk evaluation for formaldehyde.



I. Dr. Swenberg - formaldehyde DNA-reaction products in various tissues from rodents and monkeys

Formaldehyde-Induced DNA-Protein Crosslinks

- DNA-Protein Crosslinks (DPCs) have long been known to be genotoxic.
- Heck and Casanova conducted extensive studies on rats and primates exposed to radiolabeled formaldehyde.
- We have now developed a chemical-specific method for the dG-OHMe-cysteine DPC that can measure both endogenous and exogenous DPC.



Time to Steady-State for Exogenous [13CD₂]-HO-CH2-dG Adducts in Nasal Epithelium

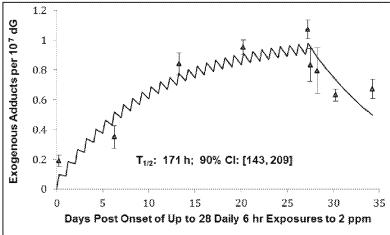


Figure 4. Estimated time for exogenous [13 CD₂]- 12 -HOMe-dG adducts to reach the steady-state concentration and 12 CD₂- 12 CD₂- 12 CD₂- 12 CD₂- 12 CD₃- 12 CD₃



Looking at Adducts originating from both endogenous and exogenous formaldehyde. 4CD-0 Exposure Tissus Collection DNA Isolation Reduction with NaCNBH, Digestion and HPLC Fractionation Nano LC-M5/M5



Formation of N^2 -HOMe-dG mono-adducts (mean \pm SD) in rat nasal epithelium, bone marrow and white blood cells exposed to 2-ppm labeled formaldehyde for 28 days.

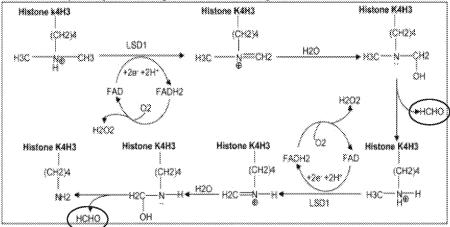
	Rat nasal epithelium N²-HOMe-dG (adducts/10 ⁷ dG)			Rat bone marrow N ² -HOMe-dG (adducts/10 ⁷ dG)		Rat white blood cells N²-HOMe-dG (adducts/10 ⁷ dG)			
Exposure period									
	Endogenous ^a	Exogenous	n	Endogenous *	Exogenous	n	Endogenous a	Exogenous	n
7 days	2.51 ± 0.63	0.35 ± 0.17	5	3.37 ± 1.56	/n.d	6	2.62 ± 1.12	/n.d.\	4
14 days	3.09 ± 0.98	0.84 ± 0.17	5	2.72 ± 1.36	nd \	6	2.26 ± 0.46	n.d.	4
21 days	3.34 ± 1.06	0.95 ± 0.11	5	2.44 ± 0.96	nd \	6	2.40 ± 0.47	n.d.	4
28 days	2.82 ± 0.76	1.05 ± 0.16	6	3.43 ± 2.20	0.34 5	12	2.49 ± 0.50	n.d.	4
28 days + 6h post expo	2.80 ± 0.58	0.83 ± 0.33	9	2.41 ± 1.14	n.d.	6	2.97 ± 0.58	n.d.	4
28 days + 24h post expo	2.98 ± 0.70	0.80 ± 0.46	9	4.67 ± 1.84	nd.	5	2.57 ± 0.58	n.d.	4
28 days + 72h post expo	2.99 ± 0.63	0.63 ± 0.12	9	5.55 ± 0.76	nd	6	1.75 ± 0.26	n.d.	4
28 days + 168h post expo	2.78 ± 0.48	0.67 ± 0.20	10	2.78 ± 1.94	nd /	4	2.61 ± 1.22	nd /	4
Air control	2.84 ± 0.54	n.d.	8	3.58 ± 0.99	nd.	6	2.76 ± 0.66	\n.d./	6

 $^{^{\}circ}$ No statistically significant difference was found using the two-sided Dunnett's test (multiple comparisons with a control) (Dunnett, 1964). $^{\circ}$ The amount of exogenous N^2 -HOMe-dG adducts that was found in only one bone marrow sample analyzed by AB SCIEX Triple Quad 6500. n.d. = not detected.



Some of the Endogenous Formaldehyde Arise from Demethylation of Histone 3 in the Nucleus

A Postulated pathway for Demethylation of diMeK4H3 by LSD1



Shi et al. Cell, 2004; 119(7):941-953. (Cited over 1,100 times)



dG-Me-Cys in Rats Exposed to High Levels of Formaldehyde

Rats Exposed to 15 ppm

Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of rats exposed to 15 ppm of formaldehyde (6 h per

Tissue	Exposure period (day)	day) Me-Cys (cro	sslink/10 ⁸ dG)
	period (ddy)	Endogenous	Exogenous
Nose	0	6.50 ± 0.30 (n=5)	ND*
	1	4.42 ± 1.10 (n=6)	5.52 ± 0.80
	2	4.28 ± 2.34 (n=6)	4.69 ± 1.76
	4	3.67 ± 0.80 (n=6)	18 18 4 7.23
PBMC	0	4.98 ± 0.61 (n=5)	/ ND /
	1	3.26 ± 0.73 (n=4)	/ ND \
	2	3.00 ± 0.98 (n=5)	ND
	4	7.19 ± 1.73 (n=5)	ND
D.	0	1.49 ± 0.43 (n=3)	ND
Bone Marrow	1	1.67 ± 0.18 (n=3)	ND
	2	1.66 ± 0.57 (n=3)	\ ND /
	4	1.41 ± 0.21 (n=3)	\ ND/

* ND, Not detected



Similar responses are seen in Primates

Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of primates exposed to 6 ppm of formaldehyde (6 h per day)

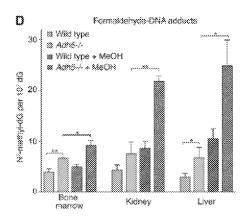
Tissue	Exposure period (day)	dG-Me-Cys (crosslink/10 ⁸ dG)		
	(,)/	Endogenous	Exogenous	
	0	2.50 : 1.01 (5)) ID	
Nose	2	$3.59 \pm 1.01 \ (n=5)$	ND	
		$3.76 \pm 1.50 \ (n=5)$	1.36 ± 0.20	
PBMC	0	$1.34 \pm 0.25 (n=5)$	ND	
TBMC	2	1.57 ± 0.58 (n=4)	ND \	
	0	2.30 ± 0.30 (n=4)	ND	
Bone Marrow	2	$1.40 \pm 0.46 \; (n=5)$	ND	
	0	15.46 ± 1.98 (n=6)	ND /	
Liver	2	11.80 ± 2.21 (n=6)	\ND /	

^{*} ND, Not detected



Formaldehyde derived DNA reaction products in various tissues from formaldehyde precursors

- ☐ A variety of compounds are metabolized to formaldehyde e.g., methanol, caffeine, aspartame, many drugs.
- ☐ Tissue formaldehyde adducts are found after with dosing mice methanol.
- ☐ With formaldehyde, no DNA-adducts are found at sites other than in the front of the nose in either rats or the non-human primates.
- ☐ Inhaled formaldehyde does not reach these other tissues



Pontel et al. Molecular Cell, 2015; 60(1):177-188



Ongoing Studies on Formaldehyde DNA-reaction products

- Low dose exposures in rats (air control, 1 ppb, 30 ppb, 300 ppb)
- Breath analysis shows approximately 1-2 ppb in humans
- 1 ppb is approximately the same as breath analysis with no exposure to formaldehyde
- Expected completion of mass spectrometry by January 2018



II. Key New Epidemiological Evidence/Analyses: NPC, AML and Mode of Action – Dr. Kenneth Mundt

- Marsh et al. (2014, 2016) challenge conclusion of NPC association as "neither consistent with the available data nor with other research findings"
 - "driven heavily by anomalous findings in one study plant (Plant 1)"
 - Nasal/sinus cancers seemed more plausible than NPC, but increased risk not seen.
- Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009)
 - Separated myeloid leukemias into acute (AMLs) and chronic (CML)
 - Associations seen with Hodgkin lymphoma and CML, but not observed in other studies
 - · Evaluated associations with "peak" exposure
- Gentry et al. (2013) and Mundt et al. (2017) reanalysis of Zhang et al. (2010) demonstrate no association between formaldehyde exposure and any reported outcome among exposed workers.



No excess mortality from AML or CML observed

Checkoway et al. 2015 Non-exposed (n=3,136) Exposed (n=22,483) Non-exposed (n=3,108) Exposed (n=22,511) Obs SMR (95% CI) Obs SMR (95% CI) Obs SMR (95% CI) Obs SMR (95% CI) 4 0.65 (0.35–1.74) 44 0.90 (0.67–1.21) 4 **0.69** (0.19-1.76) 44* **0.86** (0.64-1.16) Mveloid leukemia 4 0.93 (0.25-2.37) 30 0.80 (0.56 1.14) AML NR CML 0 13 0.97 (0.56-1.67) NR

US mortality rates used as the reference



^{*}One death was coded to ICD-8 205.9, unspecified myeloid leukemia.

Association between peak exposure and mortality using most specific diagnosis (Checkoway et al. 2015)

		No peak	2	2.0 to < 4.0 ppm		≥4.0 ppm	
Diagnosis	Obs	HR (95% CI)	Obs	HR (95% CI)	Obs	HR (95% CI)	P trend
Hodgkin Iymphoma	15	1.0 (referent)	5	2.18 (0.77-6.19)	7	3.38 (1.30-8.81)	0.01
Myeloid leukemia	27	1.0 (referent)	11	2.09 (1.03-4.26)	10	1.80 (0.85–3.79)	0.06
AML	21	1.0 (referent)	7	1.71 (0.72-4.07)	6	1.43 (0.56-3.63)	0.31
CML	6	1.0 (referent)	3	2.62 (0.64–10.66)	4	3.07 (0.83-11.40)	0.07

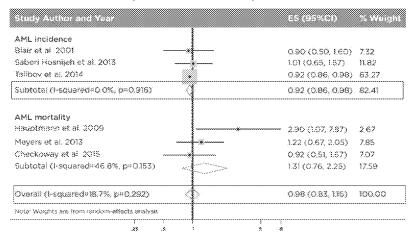
Of 13 AML deaths with peak >2.0 ppm, only 4 had any peak within the 20 years of death; only 1 AML death occurred (similar to expected) within 2 to 15 years (typical latency window).

Uncertain relevance of exposure measure – predicted peak exposure – with no measures of actual exposures



No increased risk of AML is seen in relation to occupational exposure to formaldehyde

AML studies stratified by incidence vs. mortality





More complete analysis of Zhang et al. 2010 data

- Zhang et al. (2010) reported significant "changes"* in blood parameters and aneuploidy in in vitro cell cultures.
- Concluded, "formaldehyde exposure can have an adverse effect on the hematopoietic system and that *leukemia* induction by formaldehyde is biologically plausible, which heightens concerns about its leukemogenic potential from occupational and environmental exposures."



^{*}Study was cross-sectional and reported differences in blood parameters between exposed and unexposed workers were maeasured at one point in time: no changes were investigated, over times (boldface emphasis added).

Association between formaldehyde exposure and WBC and RBC counts and components do not show expected dose-response

Exposure	Blood Count Adjusted RR	95% CI	†p-value	Blood Count Adjusted RR	95% CI	†p-value
	WBC			RBC		
Unexposed	1.00			1.00		
<1.3 ppm	*0.87	0.78-0.97		*0.94	0.91-0.98	
≥1.3 ppm	*0.85	0.76-0.96	0.943	*0.94	0.90-0.98	0.947
!	Lymphocytes			<u>Hemoglobin</u>		
Unexposed	1.00			1.00		
<1.3 ppm	*0.85	0.75-0.96		0.98	0.94-1.01	
≥1.3 ppm	*0.79	0.69-0.90	0.660	0.99	0.95-1.03	0.818
	Monocytes			MCV		
Unexposed	1.00			1.00		
<1.3 ppm	0.90	0.77-1.06		1.03	0.99-1.08	
≥1.3 ppm	0.89	0.75-1.04	0.973	1.06	1.02-1.11	0.550
	Granulocytes			Platelets		
Unexposed	1.00			1.00		
<1.3 ppm	0.87	0.75-1.01		*0.85	0.75-0.96	
≥1.3 ppm	0.88	0.75-1.03	0.997	0.91	0.80-1.03	0.674

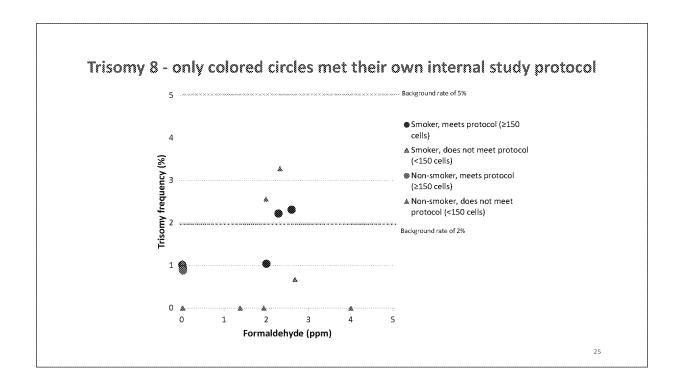
[†]Comparison between exposed categories



^{*}p<0.05 compared with unexposed

Monosomy 7 – only colored circles met their own internal study protocol 22 20 Smoker, meets protocol (≥150 cells) 18 ▲ Smoker, does not meet protocol (<150 cells) Non-smoker, meets protocol (≥150) & Non-smoker, does not meet protocol (<150 cells)</p> 6 4 Background rate of 5% ٨ 2 & ----- Background rate of 2% 0 Formaldehyde (ppm)





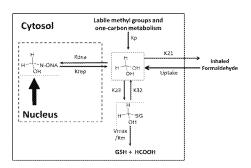


Epidemiological Conclusions

- Epidemiological evaluation of the one cluster of NPC deaths not clearly associated with formaldehyde exposure. Nasal/sino-nasal cancers seemed plausible based on animal studies but increased risk of these tumors has not been seen in the epidemiological studies.
- Conclusions relied upon from Beane Freeman et al. 2010, i.e., association between ML and 'peak' exposure were not verified upon more complete analysis:
 - · No excess of ML or AML observed; and
 - Very few decedents with AML had any peak exposure (only 1 within usual latency period).
- Conclusions relied upon from Zhang et al. 2010 inconsistent with fuller analysis of study data, including unreported individual exposure measurements: no associations with exposure level seen among exposed.
- Weight of evidence synthesis of epidemiological evidence provides vert little support for a causal association between formaldehyde and either NPC or AML.

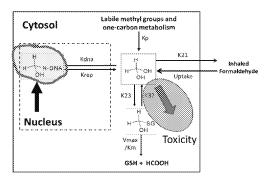


III. Integrating studies into a more quantitative risk evaluation



Background: Formaldehyde flux, primarily from tissue to air, with significant background levels of various formaldehyde reaction products

Exposed: Formaldehyde flux, primarily from air to tissue, increases tissue concentration leading to cytotoxicity and increased level of DNA-reaction products



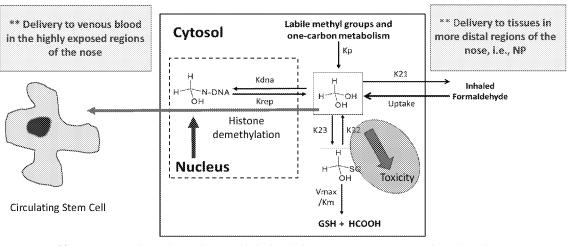


Recommendations/Conclusions: Mode of Action

- The risk assessment for formaldehyde should be structured around a MOA framework based on the extensive understanding of cancer causation in the rat nose
- Measures of DNA-reaction products from formaldehyde should be central considerations in evaluating the ability of inhaled formaldehyde to reach other tissues
- The BBDR model for formaldehyde by Conolly and others could be updated to assist in answering questions about the relative roles of cytotoxicity and DNAreactivity in cancer in the rat



What would be the proposed MOA for human cancer in light of central role of high doses and cytotoxicity?



^{**} Dosimetry studies indicate that it unlikely that high tissue concentrations can be achieved in any of these more remote tissues.



Recommendations/Conclusions: NP Cancer Epidemiology

- The association of NPC with formaldehyde exposure needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde and the presence of relatively high concentrations in all cells.
- * Review experience with other human nasal carcinogens to determine whether there are reasons to expect differential sensitivity in particular portions of the human nose compared to the rat.

Recommendations/Conclusions: LHP Cancer Epidemiology

- The association of LHP cancer also needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde adding to an already substantial level of cellular formaldehyde.
- * Evaluate experience with other other compounds producing leukemia, such as benzene and chemotherapeutic compounds, where bone marrow toxicity is also evident.



Systematic review is more than just assessing modes-of-action IPCS general scheme illustrating the main steps in evaluating the THE IPCS CONCEPTUAL MOA FRAMEWORK FOR human relevance of an animal MOA for tumour formation. **EVALUATING ANIMAL CARCINOGENESIS:** is the weight of evidence sufficient to NO Continue Introduction to the Framework Analysis establish a mode of action (MCA) in with risk assessment · Postulated mode of action (theory of the case) When we end up YES here, how do we do the quantitative · Concordance of dose-response relationships risk evaluation? Can human relevance of the MOA be reasonably excluded on the Temporal association MOA not casis of fundamental qualitative relevant differences in key events Strength, consistency and specificity of association of between animals and numans? tumour response with key events Biological plausibility and coherence NO Other modes of action Can human relevance of the MOA NO · Uncertainties, Inconsistencies, and Data Gaps be reasonably excluded on the basis Continue MOA not of cuantitative differences in either with risk relevant · Assessment of postulated mode of action kinetic or dynamic factors between animals and humans?



Recommendations/Conclusions: The Integrated Risk Evaluation:

- The risk assessment should take into account the weight of evidence for causation of a response by formaldehyde, the concentrations in air and tissues associated with these effects, and the overall evidence for particular modes of action.
- *Systematic review needs to evaluate both the qualitative evidence for various MOAs and the manner in which the studies are brought together to support extrapolation models threshold or low-dose linear in the quantitative risk assessment.
- *This type of robust evaluation appears beyond the scope of present systematic reviews that focus on toxicity rather than the support for extrapolation models based on mode of action studies.

The oarticipants



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Commentary

Six years after the NRC review of EPA's *Draft IRIS Toxicological Review of Formaldehyde*: Regulatory implications of new science in evaluating formaldehyde leukemogenicity

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ABSTRACT

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its *Draft IRIS Toxicological Review of Formaldehyde* ("Draft IRIS Assessment"), also concluding that formaldehyde causes leukemia. Peer review of the Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" (NRC 2011). They offered recommendations for improving the Draft IRIS assessment and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key recommendations made by NRC and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

1. Introduction

Classification and regulation of human carcinogens is a key component to the protection and improvement of public health. However, proper regulation of industrial chemicals hinges on both valid hazard identification and quantitative risk assessment. Increasingly, hazard identification - at least where adequate scientific evidence is available draws on critically assessing and integrating evidence across lines of inquiry including animal and human toxicology (e.g., pharmacokinetic, mechanistic studies) and epidemiology. Quantitative risk assessment requires reasonably accurate characterization of exposure, which is complicated, especially where historical measures are sparse or do not exist. Where adequate evidence from some or all of these is lacking, and where important uncertainties remain, policy-driven approaches favoring precaution are warranted. On the other hand, as evidence accumulates, more science-focused methods can be employed, reducing uncertainties, leading to sounder conclusions. Nevertheless, confident conclusions are sometimes drawn prematurely, as discussed in this commentary. Recent evaluations of formaldehyde, coupled with

improved critical review and evidence integration expectations and new, more focused scientific evaluations, illustrate the dynamic nature of scientific inquiry, the need for parallel refinement of hazard characterization, and subsequently, stronger risk assessment.

In this paper, we illustrate the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. The impetus for the new science summarized below is derived from the International Agency for Research on Cancer's (IARC) 2009 classification of formaldehyde as a known cause of leukemia in Monograph 100F (Baan et al., 2009; IARC, 2012), the US Environmental Protection Agency's (EPA's) similar classification in the *Draft IRIS (Integrated Risk Information System) Toxicological Review of Formaldehyde – Inhalation Assessment* (hereafter referred to as "Draft IRIS Assessment") (EPA, 2010), and the criticisms and recommendations presented in two National Academy of Science (NAS), National Research Council (NRC) expert reviews – one on the Draft IRIS Assessment and one on the IRIS process itself (NRC, 2011; NRC, 2014a). Various organizations and agencies have contributed to or sponsored the new science, including governments and universities, as well as industry. In revising and finalizing the Draft IRIS

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 Table 1

 Summary of major formaldehyde carcinogenicity classifications and noted scientific basis.

Year	Agency	Carcinogenicity Classification	Findings
1981	NTP (1981)	Anticipated to be a human carcinogen	Epidemiological evidence. Not discussed Toxicological evidence. One study cited (Swenberg et al., 1980). Nasal cancers: "While a full evaluation of the carcinogenicity of formaldehyde vapor must await completion of studies at the Chemical Industry Institute of Toxicology, evidence presented to date demonstrates that inhalation of formaldehyde results in a high incidence of nasal cancers in rats (Swenberg et al., 1980)."
1981 ^a	IARC (1982a; b)	Possibly carcinogenic to humans (Group 2B)	Epidemiological evidence. Inadequate (6 epidemiology studies) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to rat, causes nasal cancers.
1982	NTP (1982)	Anticipated to be a human carcinogen	Epidemiological evidence. Inadequate (cites BARC, 1982a; b) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to two strains of rats. Nasal cancers. One test in mice did not produce statistically significant results.
1987 5	IABC (1987)	Dyshobly agraineesnia to hymona	Other studies in animals (mice and hamsters by inhalation exposure) were considered inadequate for evaluation.
190/		Probably carcinogenic to humans (Group 2A)	Epidemiological evidence. Limited Nasal cancers: Reported epidemiological evidence is strongest for nasal and nasopharyngeal cancer, noted limitations with small numbers of exposed cases and inconsistent reports. Leukemia: "Excess mortality from leukemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excess for these cancers among professionals is due to conditions other than formaldehyde. The slight excesses of cancer among professionals noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level, or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies." Toxicological evidence. Sufficient No changes in information reported from IARC (1982b) Supporting data. "In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings (IARC, Suppl
1991	EPA (1991)	Probable human carcinogen (Group B1)	6, 1987)." Epidemiological evidence. Limited (28 studies considered) Nasal cancers: "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products." (p.7) Leukemia: "Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated." (p. 8) Toxicological evidence. Sufficient, nasal squamous cell carcinomas Increased incidence of nasal squamous cell carcinomas observed in rats and mice in long-term inhalation studies. Supporting data. "The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as
1994 ^c	IARC (1995)	Probably carcinogenic to humans (Group 2A)	acetaldehyde." (p. 7) Epidemiological evidence. Limited Nasal cancers: Lack of consistency between cohort and case-control studies of cancers of the nasal cavities and paranasal sinuses. Leukemia: "The studies of industrial cohorts also showed low or no risk for lymphatic or hematopoietic cancers; however, the cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by a consistent lack of excess risk for brain cancer in the studies of industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists." (p. 334) Toxicological evidence. Sufficient (nasal squamous cell carcinomas) Squamous cell carcinomas of nasal cavities, at highest exposure. No evidence of carcinogenicity in hamsters. Mice showed no effect or were inadequate for evaluation. Supporting data. Genotoxic in variety of experimental systems in vivo. Induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, gene mutation in human and rodent cells in vitro.



sister chromatid exchange, gene mutation in human and rodent cells in vitro.

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Table 1 (continued)		
Year	Agency	Carcinogenicity Classification	Findings
2004 ^d	IARC (2006)	Carcinogenic to humans (Group 1)	Epidemiological evidence. Sufficient, based on nasopharyngeal cancer Leukemia: "There is strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde. Increased risk for leukemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers." (p.276) Toxicological evidence. Sufficient (nasal squamous cell carcinoma)
			Supporting data. Mechanism for inducing myeloid leukema is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells. "The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukemia in humans." (p. 280)
2009 *	IARC (2012)	Carcinogenic to humans (Group 1)	Epidemiological evidence. Formaldehyde causes cancer of the nasopharynx and leukemia. "The Working Group was not in full agreement on the evaluation of formaldehyde causing leukemia in humans, with a small majority viewing the evidence as sufficient
			of carcinogenicity and the minority viewing the evidence as limited." (p. 430) Toxicological evidence. "Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427) "Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p.428) Inconsistent genotoxic effects in blood lymphocytes from animals exposed to formaldehyde via inhalation.
			Supporting data. "Particularly relevant to the discussions regarding sufficient evidence was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukeaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological prescursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430) "Three possible mechanisms, all focused around genotoxicity, are moderately
2010	Draft IDIS Assessment (FDA 2837)	Carcinogenic to humans	supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the mechanisms is the most important." (p. 430)
2010	Draft IRIS Assessment (EPA, 2616)	Carcinogenic to humans	Epidemiological evidence. Sufficient. "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (p. 6–46). All LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts
			(embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (p. 4–180). All leukemias as a group: "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong
			as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all
			leukemia as a group." (p. 4–182) Myleoid leukemia: "Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Pinkerton et al., 2003; Hayes et al., 1990; Stroap et al., 1996; Wairath and Fraumeni, 1984, 1983; but not Beaue Freeman et al., 2009), the
			statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia." (p. 4–185) Toxicological evidence. Limited evidence to support conclusion that
			formaldehyde exposure causes leukemia. Four studies evaluated the leukemic potential of formaldehyde. "Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Columbus Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when



exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after

Supporting data. "Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been coumented in formaldehyde exposed workers, including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells." (p. 6-22)

chronic inhalation exposures (Seliakumar et al., 1985)." (p. 6-21)

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Year	Agency	Carcinogenicity Classification	Findings
2012	NTP (2011)	Known to be a human carcinogen	Epidemiological evidence. Causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia." (p. 195) Toxicological evidence. No specific evidence cited regarding leukemia beyond the following: "Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these turmos were exposure-related, because of limitations in the reporting of these tumors (Soffritti et al., 2002)." (p. 198) Supporting data. "Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves, 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al., 2016a). Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. The endogenous concentration in the blood of humans, monkeys, and rats is about 2–3 µg/g, and the concentration does not increase after inhalation of formaldehyde from exogenous sources (Rieck et al., 1985; Casanova et al., 1988; Heck and Casanova, 2004). Moreover, N2-hydroxymethyl-dG–
2012	RAC (2012)	Carc. 1B - H50 ⁷ May cause cancer	formaldehyde to reach the bone marrow. In addition, there is some evidence that formaldehyde causes adverse haematological effects in humans." (p. 199) Epidemiological evidence. Limited "In conclusion, while some studies have found increased rates of leukemia, the epidemiology data do not show consistent findings across studies for leukemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukemia rates among embalmers, pathologist and anatomists, but not among industrial workers, suggest the possibility of confounding factors that bear investigation. Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukemia." (p.41) Toxicological evidence. "No indication of carcinogenic potential on organs/ tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumors in inhalation study of rats and mice (Kerns et al., 1983)." (p.22) Supporting data. "Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found a values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde. These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well a the skin. (888-Wissenschaft, 2006). Thus, it may be expected that carcinogenic



Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2016	Scientific Committee on Occupational Exposure Limits for Formaldehyde (Selt et al., 2016)	Carcinogen Group C (genotoxic carcinogen with a mode- of-action based threshold)	Epidemiological evidence. Limited. Leukemias: "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45) Toxicological Evidence. "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49) Supporting Data. "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49)

a IARC Working Group met February 1981. IARC Preamble (1982): "For many of the chemicals evaluated in the first 29 vol of the/ARC Monographs for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer."

- ^b IARC Working Group met March 1987.
- ^c IARC Working Group met October 1994; monograph published 1995.
- ^d IARC Working Group met June 2004; monograph published 2006.
- ^e IARC Working Group met October 2009; monograph published 2012.
- f EU harmonized classification and labelling.

Assessment (EPA, 2010), EPA now has the opportunity to incorporate the new evidence in addressing many of the issues raised by the NRC reviews.

2. Formaldehyde cancer hazard evaluation

The carcinogenicity of formaldehyde has been evaluated by several agencies since the early 1980s, including the IARC, the National Toxicology Program (NTP) of the National Institute for Environmental Health Sciences (NIEHS), the EPA, and most recently, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA), and the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission (Table 1). Except for the RAC review (RAC, 2012) and the SCOEL review (Bolt et al., 2016), which reclassified formaldehyde as a Carcinogen Category 1B (i.e., presumed to have carcinogenic potential for humans) and a Category C carcinogen (i.e., genotoxic carcinogen with a mode of action based threshold), respectively, these reviews classified formaldehyde as a known human carcinogen, primarily based on NPC but also on lymphohematopoietic malignancies (LHM) as a group and/or all leukemias as a group, and all myeloid leukemias (ML) as a group (EPA, 2010; IARC, 2012; NTP, 2011). Differences between NTP (2011) and EPA draft classifications (final version of the EPA review is pending) have been highlighted by Rhomberg (2015a) and differences between the IARC (2012) and the RAC (RAC, 2012) evaluations have been discussed by Marsh et al. (2014).

The reviews by authoritative bodies acknowledged that hazard identification for formaldehyde was not straightforward, especially with respect to possible leukemogenicity, in part due to its endogenous production and high reactivity. This prompted closer scrutiny regarding the methods used to critically evaluate the strength and quality of scientific studies, and ultimately, how best to integrate evidence across lines of inquiry such as animal, mechanistic and epidemiological evaluations.

IARC first classified formaldehyde as "carcinogenic to humans" (i.e., Group 1) in 2005 (Cogliano et al., 2005; IARC, 2006), revising the previous evaluation in 1995 that formaldehyde is "probably carcinogenic to humans" (i.e., Group 2A) (Table 1). The 2005 evaluation

(Cogliano et al., 2005; iARC, 2006) concluded that formaldehyde causes NPC, based primarily on results from animal studies, with additional evidence from "the largest and most informative cohort study of industrial workers" (i.e., Hauptmann, et al., 2004). Results from animal studies demonstrated that formaldehyde in direct contact with nasal passage tissues induced tumors at formaldehyde concentrations > 2 parts per million (ppm) as summarized by Nielsen et al. (2013) and later by Nielsen et al. (2017). This was considered consistent with formaldehyde's demonstrated genotoxicity, and with the "sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans" (IARC, 2006).

IARC (2012) concluded that formaldehyde also causes leukemia, and in particular ML, although the Working Group noted that it was a "small majority" who found the evidence to be sufficient. Neither Hauptmann et al. (2003) nor the subsequently updated study (Beane Freeman et al., 2009) published results specifically for acute myeloid leukemia (AML). The Working Group noted a study reporting aneuploidy in the blood of exposed workers (Zhang et al., 2010a), recently accepted for publication, provided supporting data, with the caveat that the study needed to be replicated (IARC, 2012). Indeed, proper replication of this study is still needed, because the study protocol was not consistent with adequate cell counting standards, including the authors' earlier descriptions of the OctoChrome FISH method (Zhang et al., 2005; Zhang et al., 2011) and other standards (American Society of Medicai Genetics, 2006). One particular challenge is that occupational exposure limits in North America, Europe and in many countries around the world protect workers from the levels of occupational formaldehyde exposures that were studied by Zhang et al. (2010a) in China making replication of the study logistically difficult. Proper replication of this study also will require use of methods to successfully distinguish between aneuploidy arising in vivo from aneuploidy that arises during the period of in vitro culture, as discussed in section 3.3.3 below.

Following the IARC review and classification, the National Toxicology Program (NTP) concluded in the 12th Report on Carcinogens (12th RoC) that formaldehyde causes nasopharyngeal cancer and myeloid leukemia (NTP, 2011) (Table 1). The 12th RoC stated "The most informative studies for evaluation of the risk of ML are the large cohort studies of industrial workers (the NCI, NIOSH, and



British cohorts) and the NCI nested case-control study[‡] of lymphohematopoietic cancer in embalmers" and specifically that "Three of these four studies found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships". However, the NTP also noted "In the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde exposure" and that in the only case-control study examining ML (Blair et al., 2000) "an excess risk was found for chronic (but not acute) myeloid leukemia" (NTP, RoC, 12th edition, "Formaldehyde", p.3).

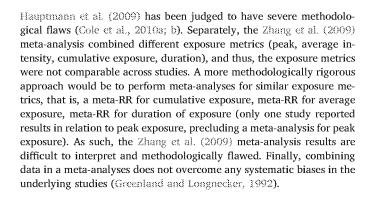
2.1. Environmental Protection Agency integrated risk assessment program (IRIS)

Formaldehyde had been classified by the EPA as a "probable" human carcinogen (Group B1) in 1991 (Table 1). An updated assessment for public review and comment was first released in June 2010, 12 years after the EPA announced the re-evaluation, and the draft assessment reported that formaldehyde causes NPC, nasal and paranasal cancer, lymphohematopoietic cancers, all leukemias, and ML (Table 1). The EPA (2010) also derived a draft inhalation unit risk (IUR) value of $8.1\,\times\,10^{-2}$ per ppm (6.6 $\times\,10^{-5}$ per $\mu\text{g/m}^3)^2$ based on the upper bound on the sum of the risk estimates for NPC, Hodgkin lymphoma, and leukemia (combined risks) based on part of the results reported in Beane Freeman et al. (2009). For rationale, the EPA said the classification "is supported by cohort analyses of embalmers, pathologists and anatomists (Hall et al., 1991; Hayes et al., 1990; Levine et al., 1984; Matanoski, 1989; Stroup et al., 1986; Walrath and Fraumeni, 1983, 1984)" despite the observation that "... SMR analyses of the large industrial cohorts do not indicate a similar association (Beane Freeman et al., 2009; Coggon et al., 2003; Pinkerton et al., 2004)" (EPA, 2010; page 4-180). The EPA also cited three meta-analyses (Bosetti et al., 2008; Collins and Lineker, 2004; Zhang et al., 2009) that largely included the same studies as providing additional evidence. Repeatedly reporting the same results, however, does not constitute independent or additional evidence. Similarly, all meta-analyses included earlier versions of the NCI cohort workers and embalmers studies and therefore, the meta-analyses, too, are redundant with the updated analyses of the NCI cohort workers and embalmers studies.

The conclusions in the Draft IRIS Assessment specific to myeloid leukemia are as follows:

"Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Hayes et al., 1990; Pinkerton et al., 2004; Stroup et al., 1986; Wairath and Fraumeni 1983, 1984; but not Beane Freeman et al., 2009), the statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia." (EPA, 2010; pages 4–184, 4–185)

Again, because of the significant overlap between Hauptmann et al. (2009) and the three PMR studies of funeral directors and embalmers (Hayes et al., 1990; Walrath and Fraumeni, 1983; 1984) these reports do not constitute independent evidence or consistency across studies.



2.2. National academies peer-review process

The NRC of the NAS, at the request of the EPA, formed an expert Committee to perform the peer-review of the Draft IRIS Assessment. Following a series of meetings during the second half of 2010, the NRC issued the final peer-review report on April 8, 2011 (NRC, 2011) as a pre-publication copy. The Committee identified numerous constructive criticisms and data gaps, and provided recommendations for improving IRIS reviews in general (NRC, 2011). Though not directly charged to evaluate the Draft IRIS Assessment conclusions, the peer review raised important questions regarding the underlying methods giving rise to several conclusions, including the basic causal conclusions:

"EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers—"all LHP cancers," "all leukemias," and "myeloid leukemias." The committee does not support the grouping of "all LHP cancers" because it combines many diverse cancers that are not closely related in etiology and cells of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas." (NRC, 2011; page 11)

The Committee concluded that EPA's claims that formaldehyde causes leukemia, ML or related hematopoietic cancers were not supported in EPA's assessment, appeared to be subjective in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion (NRC, 2011). The absence of such a framework was judged by the committee as problematic:

"As with the respiratory tract cancers, the draft IRIS assessment does not provide a clear framework for causal determinations. As a result, the conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data. Although EPA provided an exhaustive description of the studies and speculated extensively on possible modes of action, the causal determinations are not supported by the narrative provided in the draft IRIS assessment. Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to its conclusions." (NRC, 2011; page 11)

The NRC peer review further pointed out that the \mathbb{EPA} (2010) conclusion that formaldehyde causes ML was based primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action) were not considered beyond studies conducted by Zhang et al. (2009, 2010a).

In the 7th and final chapter of its review, entitled, "A Roadmap for Revision," the NRC provided recommendations in two categories: "Critical Revisions of the Current Draft IRIS Assessment of



¹ This study technically is not a "nested case-control study" but rather a pooled reanalysis of death certificate data from several published proportionate mortality ratio (PMR) analyses, using a case-control approach. Thus, it carries the same limitations of death certificate analyses performed outside of a well enumerated cohort, and therefore is not "nested" in any true cohort that could be accurately enumerated.

 $^{^2}$ This is 15 times higher than the inhalation unit risk (IUR) derived by EPA for vinyl chloride (4.4 \times 10^{-6} per $\mu g/m^3$) (EPA, 2000; page 50), a chemical for which the evidence clearly supports a causal association between exposure and effects in both animals and humans.

Formaldehyde," and "Future Assessments and the IRIS Process" (NRC, 2011). NRC (2011) specifically identified the systematic review standards adopted by the Institute of Medicine (IOM), as being appropriate for such an analysis (IOM, 2011).

Following the release of the NRC (2011) peer review, Congress issued House Report No. 112–151 (US U.S. House, 2011), and directed EPA to incorporate recommendations of Chapter 7 of the NRC (2011) peer-review report into the IRIS process. In 2014, NRC released an additional report on the IRIS process (NRC, 2014a), and emphasized the importance of evidence integration for hazard identification, in which studies of higher quality and low risk of bias are given greater weight in drawing conclusions regarding causality.

As part of their response to the NRC reviews, the EPA convened a state-of-the-science workshop on formaldehyde on April 30 and May 1, 2014 in Arlington, Virginia. This workshop focused on three themes:

- Evidence pertaining to the influence of formaldehyde that is produced endogenously (by the body during normal biological processes) on the toxicity of inhaled formaldehyde, and implications for the health assessment;
- Mechanistic evidence relevant to formaldehyde inhalation exposure and lymphohematopoietic cancers (leukemia and lymphomas); and
- Epidemiological research examining the potential association between formaldehyde exposure and lymphohematopoietic cancers (leukemia and lymphomas).

(From: https://www.epa.gov/iris/formaldehyde-workshop)

A second workshop was announced at the meeting but never convened. Since then, the EPA submitted a progress report to Congress in 2015 (EPA, 2015) in response to a request from Congress (U.S. House, 2014, p. 59). Most recently, House Report No. 114–632 (U.S. House, 2016; page 57–59) and Senate Report No. 114–281 (U.S Senate, 2016; page 62) have requested the allocation of funds for NRC to peer review the revised IRIS Toxicological Review of Formaldehyde, to ensure that recommendations raised by the NRC (2011) were implemented.

3. New studies published since the 2011 NRC peer review of the draft IRIS assessment

Numerous studies and updated analyses have been published since the 2011 NRC peer review of the Draft IRIS Assessment, the findings of which, at least in part, fill many of the "data gaps" and address several key methodological issues highlighted in the NRC Committee recommendations (NRC, 2011). Below we summarize this new research, organized around the data streams (e.g., epidemiological, toxicological, and mode of action) for evidence integration and quantification of potential leukemia risks, specifically responsive to the following NRC recommendations (2011) (page reference provided):

• Epidemiological Evidence

- Discussion of the specific strengths, weaknesses and inconsistencies in several key studies, as the draft IRIS assessment relies solely on epidemiologic studies to determine causality. (p.113)
- Clarification of the basis of the EPA's interpretations of the Beane Freeman et al. (2009) results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (p.113)
- Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (p. 113)

• Toxicological Evidence

Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (p.110)

• Mode of Action Evidence

- Improving the understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (p. 58)
- Reconciliation of divergent statements regarding systemic delivery of formaldehyde, (p.59) as direct evidence of systemic delivery of formaldehyde is generally lacking. (p.5)
- Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (p. 5)

• Dose-Response Assessment

- Independent analyses of the dose-response models to confirm the degree to which the models fit the data appropriately. (p. 14)
- Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (p.14)
- Further justification of the selection and use of the NCI cohort (Beane Freeman et al., 2009) for calculation of unit risk because the cumulative exposure metric (used in the calculation of unit risk) was not related to leukemia risk in the NCI cohort. (p.112)

• Methods for Evidence Integration

• Development of an approach to weight of evidence that includes "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (p. 113)

A summary of each of these recommendations and data gaps, along with the new science that has been conducted to address them is provided in Table 2 and discussed in the following sections.

3.1. Epidemiological evidence

The NRC peer review called attention to the EPA's sole reliance on epidemiological studies to determine causality, rather than integrating epidemiology data with the toxicological and mechanistic evidence. When inferring causation from epidemiology studies, the evidence is critically assessed and synthesized across a body of individual studies, with greater weight assigned to studies of higher quality (rather than assigning equal weight to each). Better epidemiological studies are those that implement individual level exposure data, and minimize the potential for systematic bias and confounding. The ascertainment of outcome and analysis using accurate (and specific) diagnosis are also critical in the causal evaluation. The NRC peer review noted that the grouping of "all LHPs" comprises 14 biologically distinct diagnoses in humans and should not be used in determinations of causality. There is some evidence that these diseases may originate from the same stem cell line (Gluzman et al., 2015; Goldstein, 2010) and could therefore arise from direct effects on these cells. There are no studies, however, that demonstrate an effect on these stem cells following exposure to formaldehyde. The largest population of these stem cells would be found in the bone marrow, and, based on the available evidence, inhaled formaldehyde appears incapable of reaching the bone marrow (see Section 3.3.2). The affected cells would need to be circulating stem cells that encounter formaldehyde at the portal of entry (i.e., the nose or upper airways) and then return to the bone marrow.

After the NRC peer review was published, Checkoway et al. (2012) critically reviewed the epidemiological evidence and reported inconsistent and sporadic associations between formaldehyde exposure and various specific LHM, including ML. Only a few epidemiology studies considered AML specifically. Since the critical review (Checkoway et al., 2012), several additional epidemiological studies have been published that provide insights on formaldehyde exposure and AML risk and address other specific issues raised by the 2011 NRC peer review. The key strengths and limitations of these studies are highlighted below.



Table 2 Summary of NRC (2011) comments or identified data gaps and new formaldehyde science by lines of inquiry.

NRC (2011) Comment/Identified Data Gap

New Formaldehyde Science

A. Epidemiological Evidence

- Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (NRC, p. 113)
- Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. (NRC, p. 113)
- Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (NRC, p. 112–113)
- The selection and use of the NCI cohort (Beans Freeman et al., 2009) should be further justified. (NRC, p. 112)

B. Toxicological Evidence

- Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (NRC, p. 110)
- C. Mode of Action Evidence
- Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (NRC, p. 58)
- Reconcile divergent statements regarding systemic delivery of formaldehyde (p.59); direct evidence of systemic delivery of formaldehyde is generally lacking. (NRC, p.5)
- Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (NRC, p. 5)

- New analyses of the NCI formaldehyde workers cohort specifically for AML are reported.
 Results do not support the hypothesis that formaldehyde causes AML. See: Checkoway et al., 2015
- Associations seen between formaldehyde exposure and Hodgkin lymphoma and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. See: Checkoway et al., 2015
- A critical review of the epidemiological literature indicated no consistent or strong
 epidemiologic evidence that formaldehyde is causally related to any lymphohematopoetic
 malignancies. The absence of established toxicological mechanisms further weakens any
 arguments for causation. See: Checkoway et al., 2012
- Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure, and few deaths occurred within 20 or more years of last peak exposure. Suggestive associations with peak exposure were observed for chronic myeloid leukemia, based on very small numbers. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (p_{trend} = 0.05) and peak (p_{trend} = 0.003) exposures. However, no other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. See: Cherkoway et al., 2015
- Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941–2012. Results provide no support for an increased hazard of myeloid leukemia from formaldehyde exposure. See: Coggon et al., 2014
- Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results
 demonstrated limited evidence for formaldehyde exposure and any LHM including AML,
 based on 14 observed cases. See: Mayers et al., 2013
- No cases of leukemia or lymphohematopoietic neoplasia were seen. FA inhalation did not cause leukemia in genetically predisposed C3B6·129F1-Trp53tm1Brd mice. See: Morgan et al., 2017
- FA inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. See: Morgan et al., 2017
- Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake
 predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was
 predicted at lower exposure concentrations. See: Schroeter et al. (2014)
- With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. See: Ya et al., 2015
- Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. Also, new evidence suggests that endogenous formaldehyde in bone marrow is toxic and carcinogenic, and may cause leukemia (but not exogenous formaldehyde). See: Lai et al., 2016; Poutsi et al., 2015; Yu et al., 2015; Edrissi et al., 2013; Moeller et al., 2011; La et al., 2011.
- Critical review of the genotoxicity literature found no convincing evidence that exogenous
 exposures to FA alone, and by inhalation, induce mutations at sites distant from the portal
 of entry tissue as a direct DNA reactive mutagenic effect specifically, not in the bone
 marrow. Review of the existing studies of hematotoxicity, likewise, failed to demonstrate
 myelotoxicity in any species– a probable prerequisite for leukemogenesis. See: Albertini
 and Raden 2016
- Reanalysis of selected raw data from the Zhang et al. (2010a) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect *in vivo* events, the reanalysis of the results provided by Zhang et al. (2010a) raise sufficient questions that limit the use of Zhang et al. (2010a) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. See: Gentry et al. (2013)
- Additional analyses were performed on the study data obtained from the original study (Zhang et al., 2010a) including individual average formaldehyde exposure concentration measurements performed for each exposed worker. The objective was to evaluate haematological parameters and aneuploidy in relation to quantitative exposure measures of formaldehyde. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Furthermore, among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk. See: Mundit et al., 2017
- The documentation of the methods applied in the Draft IRIS Assessment (EPA, 2010) lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the NCI cohort study (Beane Freeman et al., 2009). This (continued on next page)

D. Dose-Response Assessment

Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. (NRC, p. 14)



Table 2 (continued)

NRC (2011) Comment/Identified Data Gap

New Formaldehyde Science

- lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. See: Van Landingham et al., 2016
- Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. Work in progress: Clewell et al., unpublished
- Results of the "bottom-up" approach indicate that recent top-down risk extrapolations
 from occupational cohort mortality data for workers exposed to formaldehyde are overly
 conservative by substantial margins. See: Start and Swenberg, 2013
- Updated "bottom-up" risk estimates heighten the marked contrasts that are present between
 the previous estimates and the corresponding USEPA estimates, with the larger difference
 for leukemia being due primarily to the significantly improved detection limit for the
 analytical method used in quantitating DNA adduct numbers. See: Starr and Swenberg, 2016
- A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode-of-action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. See: Rhomberg et al., 2011
- Additional frameworks have been developed to integrate evidence. See: Adami et al., 2011;
 Lavelle et al., 2012; Linkov et al., 2015; Rhomberg 2015b; Rooney et al., 2014; Woodruff and Sutton. 2014.
- Other agencies or advisory bodies have conducted assessments of the carcinogenicity of formaldehyde in a transparent manner. Sec. BAC, 2012; Bolt et al., 2016; Nielsen et al., 2017

- BBDR models developed by Conolly and co-workers should be used. (p.58) These models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. (NRC, p.57)
- Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (NASNRC, p.14)

E. Methods for Evidence Integration

EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence." Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (NRC, p. 113)

3.1.1. Key studies and their strengths and limitations

Since the update of mortality in the US formaldehyde users and producers cohort (Beane Preeman et al., 2009), two other large industrywide cohort mortality studies have been updated: the NIOSH garment workers (Meyers et al., 2013) and the UK industry-wide formaldehyde producers and users (Coggon et al., 2014). In addition, a large population registry-based case-control study of incident AML cases in the Nordic countries, a small occupational study in Italy and a large multicenter European study of occupational exposures in a cohort established to study nutritional and metabolic risk factors in cancer risks have been published (Pira et al., 2014; Saberi Hosnijeh et al. 2013; Talibov et al., 2014).

3.1.1.1. NIOSH cohort study of garment workers. Meyers et al. (2013) updated mortality from 1960 through 2008 for 11,043 US garment workers exposed to formaldehyde who worked for at least three months between 1955 and 1983 at three US factories. A total of 36 leukemia deaths was reported (SMR = 1.04, 95% CI 0.73-1.44, compared to US mortality rates), of which 21 were ML (14 AML, 5 chronic myeloid leukemia (CML), 2 other and unspecified ML). Although this study did not link quantitative estimates of formaldehyde exposure to study subjects, an industrial hygiene survey during the early 1980s reported that formaldehyde concentrations were similar across all departments and facilities, and the overall geometric mean was 0.15 ppm with a geometric standard deviation of 1.90 (Stayner et al., 1988). The formaldehyde resins used to treat permanent press fabrics had been reformulated over time, and as a result, the formaldehyde concentrations measured in the early 1980s were believed to be lower than the approximately 4 ppm estimated by NRC for years prior to 1970 (NRC, 2014b). Meyers et al. (2013) reported an SMR for AML of 1.22 (95% CI 0.67-2.05), noting that NIOSH investigators "continue to see limited evidence of an association between formaldehyde and leukemia" and that "the extended follow-up did not strengthen previously observed associations." All 14 AML deaths occurred 20 or more years after first exposure to formaldehyde. The NIOSH study is a large cohort with adequate follow up but limited industrial hygiene measurements of historical formaldehyde concentrations, as most workers were first exposed prior to 1970. Therefore, the study did not assign individual estimates of cumulative or peak exposure, and analyses for mortality due to various LHM including AML were performed using duration of exposure as a proxy for cumulative exposure. Information on smoking was also lacking.

3.1.1.2. Registry-based case control study of AML in Nordic countries. Talibov et al. (2014) analyzed 15,332 incident cases of AML diagnosed in Finland, Norway, Sweden, and Iceland from 1961 to 2005. The investigators matched 76,660 controls to cases by year of birth, sex, and country. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (hazard ratio (HR) 0.89, 95% CI 0.81-0.97 for workers exposed to ≤0.171 ppm-years; HR 0.92, 95% CI 0.83-1.03 for workers exposed to 0.171-1.6 ppm-yrs, and HR 1.17, 95% CI 0.91–1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde). The strengths of this study were its exposure assessment based on a validatedJEM and the comprehensive ascertainment of incident AML cases (i.e., not deaths), resulting in high statistical power to detect increased risks, avoidance of survival bias, and the ability to consider and control for other possible leukemogens. One major limitation is the lack of data on smoking, which also is known to cause leukemia. This study failed to find an association between benzene and AML; however, increased risk of AML may be limited to those with exposure to very high concentrations that historically occurred only in a few occupational settings, e.g., the rubber hydrochloride industry (Infante et al., 1977; Schnatter et al., 2012).

3.1.1.3. European prospective investigation into cancer and nutrition (EPIC) cohort study. Saberi Hosnijeh et al. (2013) followed 241,465 subjects from 1992 through 2010 for a prospective study of lymphoid and myeloid leukemia risk in relation to occupation, nutrition and



metabolic risk factors. The European Prospective Investigation into Cancer (EPIC) investigators studied occupational risk factors among 477 incident leukemia cases (201 ML, including 113 AML, 237 lymphoid leukemia, and 39 other or unspecified leukemias) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy (Saberi Hosnijeh et al., 2013). Occupational exposures were estimated using a general population JEM that classified occupational codes of study subjects by categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). However, the authors reported that work histories were missing on a large number of cohort members, and these individuals had to be excluded. Study investigators lacked detailed job histories (job tasks and duration) for others, and the resulting exposure misclassification would be expected to be nondifferential, attenuating risk estimates. On the other hand, this is one of the few studies examining specific subtypes of leukemia with risk estimates adjusted for smoking and other risk factors. AML risk was not increased among the formaldehyde low-exposure group (HR 1.01, 95% CI 0.65-1.57) after adjusting for sex, smoking status, alcohol intake, age at recruitment and country, and no AML cases occurred among individuals in the high-exposure category. An HR for chronic lymphocytic leukemia of 1.45 (95% CI 0.46-4.56) was reported among those with high exposure to formaldehyde, but this was based on 3 or fewer cases. ML risks were increased among those employed in chemical laboratories and shoe and leather workers, and weakly increased among those exposed to benzene but not those exposed to ionizing radiation (Saberi Hosnijeh et al., 2013).

3.1.1.4. UK formaldehyde users and producers cohort study. Coggon et al. (2014) updated mortality through 2012 for the UK cohort of 14,008 formaldehyde users and producers; however, the analysis grouped all ML and did not analyze AML mortality separately. Similar to other large industrial cohorts (Beane Freeman et al., 2009; Meyers et al., 2013), industrial hygiene measurements were not available in the early years and investigators estimated averages for job titles based on irritant symptoms and later measurements. Exposures were estimated to range from background (< 0.1 ppm), low exposure (0.1-0.5 ppm), moderate exposure (0.6-2.0 ppm) and high exposure (> 2 ppm). These exposure categories were similar to those estimated by Stewart et al. (1986) and applied in Beane Freeman et al. (2009). Moreover, a larger proportion (and greater number) of the UK cohort was exposed to high concentrations of formaldehyde (approximately 18% of the cohort) than the US cohort (approximately 4% of the cohort). Coggon et al., 2014 reported no increased mortality from ML (SMR 1.16, 95% CI 0.60-2.20 for background exposure; SMR 1.46, 95% CI 0.84-2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450-1.82 for high exposure). In a nested case-control analysis of 45 ML (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was non-statistically significantly increased among workers exposed to high concentrations for < 1 year (OR 1.77, 95% CI 0.45-7.03), workers exposed to high concentrations ≥ 1 year showed no increased risk (OR 0.96, 95% CI 0.24-3.82) (Coggon et al., 2014).

3.1.1.5. Extended analysis of the NCI cohort study to evaluate specific types of myeloid leukemia. Checkoway et al. (2015) obtained the data from the NCI formaldehyde industrial workers cohort to further investigate specific types of leukemias, including AML (which had never been reported for this cohort), as well as performing an alternative analysis of peak exposure. The investigators reported that AML mortality was unrelated to cumulative exposure or peak exposure. Twelve of 34 AML deaths and 6 of 13 CML deaths occurred among study subjects with less than one year of employment. For workers employed at least one year, the risk of AML was highest (but not statistically significant) among workers with peak exposures of ≥ 2.0 to < 4 ppm (HR 1.78, 95% CI

0.61–5.25) and no trend was seen with increasing category of peak exposure (p for trend 0.37). In contrast, CML risks were greater, although the estimates were imprecise (HR 4.83, 95% CI 0.64–36.42 for peak exposure \geq 2.0 to < 4 ppm based on 2 CML deaths and HR 5.32, 95% CI 0.81–34.90 for peak exposure \geq 4 ppm based on 2 CML deaths).

3.1.2. Synthesis of epidemiology studies: exposure assessment issues identified by NRC

One of the major issues highlighted by the NRC peer review is that one exposure metric (peak exposure) was used to determine causality in the draft IRIS assessment, while a different exposure metric (cumulative exposure) was used for the dose-response evaluation to calculate an inhalation unit risk.

The NRC (2011) review of the Draft IRIS Assessment stated "the reliance on the peak exposure metric to determine causality rather than the more conventional dose metric of cumulative exposure should be further justified particularly in the absence of established modes of action" [p.112]. NRC further elaborated:

"In the absence of evidence regarding exposure-disease mechanisms, as in the case of formaldehyde and LHP cancers, cumulative exposure is typically the default dose metric applied in epidemiologic analyses and risk assessment. But the most significant results were found for peak exposures, which have the greatest associated uncertainty. In view of the importance of this study, EPA should clarify the basis of its interpretations of the results regarding the various dose metrics and the various LHP cancers. Despite those concerns, the committee agrees that the NCI study is the most appropriate available to carry forward for calculation of the unit risk." (NRC, 2011, pp. 112–113)

The NRC recommended that the quality of exposure assessment relied upon in epidemiological evaluations should be explicitly evaluated when weighting and synthesizing epidemiological evidence. Where known causal relationships have been observed, exposure-response relationships often are seen with various exposure metrics, with stronger associations seen when more relevant metrics and exposure time windows are examined. Results such as those reported by Beane Preeman et al. (2009) are a good example of conflicting findings: the conventional exposure metric, cumulative exposure, demonstrated no association with risk of ML, whereas a surrogate of 'peak' exposure suggested one (Beane Freeman et al., 2009). When evaluating differences between cumulative exposure and peak exposure, and comparing risks associated with these, several differences should be highlighted.

NCI investigators (Beane Freeman et al., 2009; Blair et al., 1986; Hauptmann et al., 2003) defined peak exposure as the maximum peak, and the NCI investigators substituted the time-weighted average (TWA) for jobs without assigned peak exposures (Stewart et al., 1986). The authors reported a significant test for trend between peak formaldehyde exposure and leukemia, but only when unexposed subjects were included. Increased risk was not seen for higher peak exposure categories (2.0 to < 4.0 ppm, or ≥ 4.0 ppm) when compared to the lower peak category (> 0 to < 2.0 ppm). No association was reported with frequency of peak exposure, average intensity of exposure or with cumulative exposure to formaldehyde ("There was little evidence among formaldehyde workers of association for any lymphohematopoietic malignancy (LHM) with average intensity or cumulative exposure at the end of follow-up in 2004." (Beane Freeman et al., 2009, p. 751). In fact, a 10% deficit of ML deaths (acute and chronic types combined) was reported when compared to US population mortality rates. In an internal analysis, Beane Freeman et al. (2009) reported that ML deaths were not associated with the number or frequency of peaks. If there were a true association between peak exposure and leukemia, one would expect to see an association with number of peaks and not only ever having a (perhaps single) peak exposure. Hauptmann et al. (2003) acknowledged that "no measurements of peak exposure were available

in this study. Peak exposures were therefore estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average" (Hauptmann et al., 2003, p. 1616; Stewart et al., 1986). Stewart et al. (1986) reported that the exposure reconstruction included rating confidence (i.e., confident, less confident, not confident) in the exposure estimate; however, the "confidence" category appeared to apply to the "rank" exposure and not the "peak exposure." For example, if an IH specified "not confident" for an average exposure estimate, it is not clear how or if this information applied to the estimate of peak exposure (categorized during data collection as 1 = none, 2 = 0.1–0.5, 3 = 0.51–2.0, 4 = 2.1–4.0, 5 = > 4.0, 9 = unknown) (Stewart et al., 1986).

In extended analyses of the NCI cohort study, Checkoway et al. (2015) refined the classification of peak exposure. Workers who did not work in jobs identified as likely having peak exposures were classified as not exposed to peaks, and became the referent group. A total of 3478 cohort members were classified as having worked in jobs with estimated peak exposure of 2- < 4 ppm, and 2907 worked in jobs with estimated peak exposure of ≥4 ppm. Analysis by ML subtype (i.e., AML and CML deaths, separately) found no association between peak exposure and AML mortality (HR 1.71, 95% CI 0.72-4.07 and HR 1.43, 95% CI 0.56-3.63, respectively) (Checkoway et al., 2015). However, 13 of the 34 AML deaths were classified as having worked in jobs likely having peak exposure > 2.0 ppm, only 4 of which worked in these jobs within the 20 years preceding their AML death (i.e., latest exposure), and only one occurred (similar to the number expected) within the typical AML latency window of 2-15 years. Upon fuller analyses of these data, Checkoway et al. (2015) subsequently found that only a third of all the AML deaths were among cohort members assigned to categories with any peak exposure (i.e., > 2.0 ppm), nearly all of whom had their last peak exposure more than 20 years earlier, well outside of the maximum latency window.

Coggon et al. (2014) also reported that limited IH data were available for the UK formaldehyde users and producers cohort, preventing the derivation of quantitative metrics. Nevertheless, the investigators expressed high confidence that the high exposure category corresponded to average concentrations of at least 2 ppm. Industrial hygiene data also were limited in the US NCI industrial workers study, although the investigators used them as part of a detailed exposure reconstruction using best practices for such a reconstruction at the time. Stewart et al. (1986) reported that historical exposure levels were estimated because most companies did not begin sampling until the mid-1970's: they also monitored "present day" (i.e., early 1980's) operations to help extrapolate historical exposures. The NCI investigators relied upon exposure rank (six levels of TWA): trace, < 0.1 ppm, 0.1–0.5 ppm, 0.51–2.0 ppm and > 2 ppm.

One criticism leveled at the UK worker cohort study (Acheson et al., 1984; Coggon et al., 2003, 2014; Gardner et al., 1993) was that the "authors reported a concern about the quality of data when they made exposure assignments" (NRC, 2014b). This criticism seems to stem from the appropriate identification and discussion of study limitations by earlier UK investigators: Gardner et al. (1993) reported "when jobs were being placed into qualitative categories of exposure in the British study, some disagreement occurred as to which of two adjacent grades was most appropriate-for example, high or moderate? To achieve consistency across all the factories, the higher of the two was always used. It is not clear how differences were resolved in the United States study." Thus, there are no essential differences in the approach used by the UK investigators and the US investigators: both studies reported that limited data were available on quantitative exposure measures using existing industrial hygiene data (from the 1980s); both exposure assessments allowed for the consideration of changes in processes and exposure controls during the period of the study; and both used ranked categories of exposure, developed before the estimation process, based somewhat on subjective sensory experiences encountered in the job (e.g., odor occasionally present), and both used eye irritation and odor

throughout the day to identify the highest intensity of exposure jobs (Acheson et al., 1984; Stewart et al., 1986).

Ultimately, the Beane Freeman et al. (2009) study alone does not (and cannot) provide reliable support for a conclusion that peak formaldehyde exposure causes ML or AML, especially considering the absence of peak measurement data in the US study, the results of the reanalysis by Checkoway et al. (2015), and the updated results from the UK study (Coggon et al., 2014), which used a more conservative approach to exposure estimation.

3.1.3. Synthesis of epidemiology studies: evaluation of the most specific diagnosis

The NRC (2011) raised the issue that diverse types of leukemias and lymphomas should not be grouped "because it combines many diverse cancers that are not closely related in etiology and cells of origin. Although the draft IRIS assessment explores specific diagnoses—such as AML and CML, as well as Hodgkin lymphoma and multiple myeloma (see, for example, EPA 2010, Tables 4-92)—the determinations of causality are made for the heterogeneous groupings of "all LHP cancers," "all leukemias," and "ML". When results for heterogeneous groupings are presented, there is no evidence of increased risk of all LHP cancers (Meyers et al., 2013; Beane Freeman et al., 2009) or all leukemias combined (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009) in industrial cohorts when compared to general mortality rates. In addition, there is no evidence of exposure-response associations between all LHPs combined (or all leukemias combined) and cumulative exposure or average exposure (Beane Freeman et al., 2009) or duration of exposure (Meyers et al., 2013; Coggon et al.,

Interestingly, the Draft IRIS Assessment noted that "Acute leukemias (ALL and AML), believed to arise from transformation of stem cells in the bone marrow, are less plausible. In contrast chronic lymphatic leukemia, lymphomas, multiple myelomas (from plasma B cells), and unspecified cancers may involve an etiology in peripheral tissues to include cells, cell aggregates, germinal centers, and lymph nodes. An association of these cancers to an exogenous agent acting at the POE [portal of entry] is biologically plausible" (EPA, 2010; page 4–190).

While the etiologies of most LHM are poorly understood, the possible role of environmental agents is plausible for AML, which has been linked with benzene, tobacco smoking, ionizing radiation and various cancer treatment agents, such as cisplastin, all of which have been classified by IARC as known human carcinogens that cause AML. It should be stressed that evidence exists that these agents, or their carcinogenic components, are capable of reaching the bone marrow. However, only six epidemiological studies of workers substantially exposed to formaldehyde published to date have published AML-specific results (Blair et al., 2001; Checkoway et al., 2015; Hauptmann et al., 2009; Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014), four of which were not available at the time of the IARC review or the release of the Draft IRIS Assessment. Saberi Hosnijeh et al. (2013) reported no association between "low" formaldehyde exposure and incidence of myeloid leukemia (HR 1.02, 95% CI 0.72-1.42 based on 49 cases exposed to formaldehyde and 130 unexposed cases). No differences were seen between subtypes: AML (HR 1.01, 95% CI 0.65-1.57) or CML (HR 0.92, 95% CI 0.46-1.84). No myeloid cases (and therefore no AML cases or CML cases) occurred among those classified as having "high" formaldehyde exposure (Saberi Hosnijeb et al., 2013). Talibov et al. (2014) found no association between formaldehyde and incident AML, after adjusting for exposure to specific solvents and ionizing radiation (HR 1.17, 95% CI 0.91-1.51 for 136 workers and 628 controls exposed to > 1.6 ppm-yrs). Meyers et al. (2013) reported a SMR for AML of 1.22 (95% CI 0.67-2.05) based on 14 observed AML deaths. Checkoway et al. (2015) performed AML-specific analysis using the NCI cohort, which had provided results only for all ML combined (Beane Freeman et al., 2009). When compared to US referent rates, AML mortality risk was decreased among workers

exposed to formaldehyde (SMR 0.80, 95 %CI 0.46–1.14) and internal analysis of exposure reported no trend with increasing cumulative exposure or peak exposure categories (Checkoway et al., 2015). Thus, new analyses of the NCI formaldehyde workers cohort specifically for AML detract from the hypothesis that formaldehyde causes AML.

The associations reported by Beane Freeman et al. (2009) between formaldehyde exposure and Hodgkin lymphoma and CML have not been observed in other studies (Meyers et al., 2013; Saberi Hosnijeh et al., 2013) and are less plausible, given the lack of known associations with Hodgkin lymphoma or CML and other chemicals or agents, such as benzene (Checkoway et al., 2015). Saberi Hosnijeh et al. (2013) reported a RR of 0.92 (95% 0.46 to 1.84) based on 46 CML cases. Meyers et al. (2013) reported a SMR of 1.35 (95% CI 0.44–3.15), based on 5 CML cases through 2008. The absence of established toxicological mechanisms for formaldehyde exposure and any of the LHM further weakens arguments for causation (Checkoway et al., 2012, 2015), especially given that inhaled formaldehyde appears incapable of reaching the bone marrow (discussed in Section 3.3).

3.2. Toxicological evidence

3.2.1. Animal evidence of formaldehyde-induced LHM

With regard to animal evidence of formaldehyde-induced LHM, the Draft IRIS Assessment (EPA, 2010) stated that the available animal evidence is limited, discussing mainly the results from the Battelle Columbus Laboratories (1981) study. The Draft IRIS assessment indicated that this study provides the only evidence of formaldehyde-induced LHM in animal models. However, the NRC (2011) peer review noted that although intriguing, EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981) contributed little to the weight of evidence evaluation.

In rats, Battelle Columbus Laboratories (1981) reported the incidence of leukemia (most of which were diagnosed as undifferentiated leukemia found sporadically in various organs) in male and female Fischer 344 rats following exposure to concentrations of 0, 2, 6, or 15 ppm for 24 months, followed by 6 months with no exposure. No concentration-related increases in the incidences of leukemia in either sex of rats were reported by Battelle Columbus Laboratories (1981), when a standard Fisher-Irwin exact test was applied (males $p=0.0972;\, \rm females\,p=0.2316).$

Because of a significant number of early deaths in the high concentration group of both males and females, Battelie Coinmbus Laboratories (1981) also applied Tarone's extension to the Cox log-rank test (Tarone, 1975) to evaluate the leukemia incidence data. This test accounts for the number of animals at risk at each time point when the response of interest is observed. This adjustment assessed the probability of developing the endpoint of interest in those animals that did not survive until the termination of the study. The results of Tarone's extension indicated that the incidence among female rats in the high concentration group was statistically significant (p = 0.0056, not 0.0003 as reported³); however, no association was seen in the male rats exposed at high concentrations (p = 0.6891). No concentration-related increase in leukemia was observed in the female rats exposed at either 2 ppm or 6 ppm, and no survival problems were noted. Even after application of Tarone's extension, leukemia in male or female rats was not identified in the Battelle Columbus Laboratories (1981) study as an endpoint related to formaldehyde exposure, nor was it so designated in two publications citing this study (Keras et al., 1983; Swenberg et al.,



More contemporary statistical methods, such as the Cochran-Armitage and the Poly3 (Bailer and Portier, 1988; Peddada and Kissling, 2006) trend tests, have replaced those used in the early 1980's. The Poly3 trend test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take inter-group survival differences into account. Importantly, the Poly3 test is the test currently used by the National Toxicology Program (NTP) to evaluate incidence data both for trend and pair-wise comparisons, to assess the probability of the response in the presence of inter-current mortality. The results of the application of these tests indicated p values of 0.43 and 0.82 for the Poly3 and Cochran-Armitage, respectively, demonstrating no association.

In mice, the Draft IRIS Assessment (EPA, 2010) suggested that the "adjusted" incidence of lymphoma in female mice, when the 6-month sacrifice animals were removed from consideration (because tissues outside of the respiratory tract were not examined), was statistically significant (p < 0.05) in animals exposed to 15 ppm formaldehyde, compared to untreated controls. However, as indicated in the methods for the Battelle Columbus Laboratories (1981) study, statistical significance, when applying the Tarone extension of the Cox test, is achieved with a p value of 0.05 divided by the number of dose groups. In the case of the Battelle Columbus Laboratories (1981) study for the mouse data, statistical significance would be p < 0.0167, as noted in the summary tables (Table 8 of the Battelle Columbus Laboratories (1981) report); therefore, based on this criterion, this endpoint was not considered statistically significant. As with the leukemia incidence in rats, the Battelle study authors did not report lymphoma in mice as an endpoint related to formaldehyde exposure.

Since 2010, two short-term carcinogenicity studies have been conducted and published (as a Technical Report) by the NTP of NIEHS in strains of genetically predisposed mice (male C3B6·129F1-Trp53tm1Brdp53 haplo-insufficient mice and male B6.129-Trp53tm1Brd) (Morgan et al., 2017). These short-term carcinogenicity studies were conducted to test the hypothesis that formaldehyde inhalation would result in an increased incidence and/or shortened latency to nasal and lymphohematopoietic tumors and to investigate hypotheses that formaldehyde may induce leukemia by a mechanism not involving DNA adduct formation. This proposed mechanism assumes that inhaled FA could cause significant genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. These damaged stem cells could reach the general circulation, home to tissues that support the hematopoietic niche, undergo lodgement and become leukemic stem cells. The animals were exposed to 7.5 or 15 ppm formaldehyde 6 hours/day, 5 days/week, for 8 weeks. The investigators reported that because the doubling time for hematopoietic stem and progenitor cells (HSPCs) is between 2 and 4 weeks, and the entire HSPC pool turns over every 8 weeks, an 8 week exposure duration was considered sufficient to investigate the hypothesized mechanism for inducing leukemia. Following the 8-week inhalation exposure, mice were monitored for approximately 32 weeks (until approximately 50 weeks of age). At the highest concentrations, significant cell proliferation and squamous metaplasia of the nasal epithelium were observed; however, no nasal tumors were observed. No cases of leukemia were seen in either strain and a low incidence of lymphoma in exposed mice was not considered related to exposure. In addition, no significant changes in haematological parameters were noted. Under the conditions of these studies, the authors concluded that formaldehyde inhalation did not cause leukemia in these strains of genetically predisposed mice (Morgan

Overall, the weight of evidence from animal studies reported in the Draft IRIS Assessment (EPA, 2010) did not support an association between formaldehyde exposure and LHM. Since that time, additional studies (Morgan et al., 2017) have provided evidence that suggests a lack of association between formaldehyde exposure and LHM. In addition, no evidence of changes in blood parameters that might be



³ This appears to be a misreading of the Battelle report. In the Battelle Report Volume A Table 10 – Analysis of Effects of Formaldehyde in Female Rats - reports a p-value of 0.0056 from the Adjusted Cox/Tarone pair-wise comparison of the control to 15 ppm for Leukemia, all. The next row in that table with an endpoint of Uterus, Endometrial Stromal Polyp is the one that reports a p-value of 0.0003 for the pair-wise analysis of control to 15 ppm.

associated with leukemias has been reported in any animal studies exposed to formaldehyde at high concentrations following both acute and chronic durations (Appelman et al., 1988; Dean et al., 1984; Johannsen et al., 1986; Kamata et al., 1997; Kerns et al., 1983; Til et al., 1988, 1989; Tobe et al., 1989; Vargova et al. 1993; Woutersen et al., 1987). Among these studies, Vargová et al. (1993) reported *increased* red blood cell counts and *increased* proportions of lymphocytes and monocytes in rats, rather than decreases, following exposure to formaldehyde by gavage at 80 mg/kg/day for 28 days.

3.3. Mode of Action Evidence

3.3.1. Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations

NRC (2011) recommended that one key improvement to the science would be an understanding of when exogenous formaldehyde exposure altered normal endogenous formaldehyde concentrations. Because formaldehyde is endogenously present, it is important to differentiate levels that are due to normal metabolic processes from levels that might be present as a result of exogenous exposure. A number of studies have applied sensitive methods to differentiate exogenous and endogenous levels of formaldehyde in tissues (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011).

The results of these studies with highly sensitive instruments and accurate assays indicate that inhaled formaldehyde was present in the nasal respiratory epithelium, but not other tissues beyond the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively (Yu et al., 2015).

An additional study conducted in rats exposed to ¹³C-formaldehyde (Kleinnijenhuis et al., 2013) provided results consistent with those from studies focused on measuring endogenous versus exogenous DNA adducts. In this study, Sprague-Dawley rats were exposed nose-only to 10 ppm ¹³C-formaldehyde for 6 hours and blood concentrations evaluated during exposure and for 30 minutes following exposure. This study was conducted specifically to investigate the mechanism proposed by Zhang et al. (2010a) that formaldehyde is absorbed during respiration and could reach any target tissue, such as the bone marrow, via the blood in the form of methanediol to exert its genotoxic activity. Exogenous ¹³C-formaldehyde was not detectable in the blood of rats either during or up to 30 min after the exposure. The authors concluded that "it is highly unlikely that the mechanism proposed by Zhang et al. (2009), that exposure to FA by inhalation may lead to an increased FA concentration in blood and as such may cause leukemia, is true" (Kleinnijenhuis et al., 2013).

New studies have been conducted to investigate the potential toxicity/carcinogenicity of endogenous formaldehyde. The most recent studies demonstrate that endogenous formaldehyde in bone marrow is toxic, and probably carcinogenic, and therefore may increase leukemia risk (Pontel et al., 2015; Lai et al., 2016).

3.3.2. Reconcile divergent statements regarding systemic delivery

Multiple studies in rats (Lu et al., 2011; Yu et al., 2015; Edrissi et al., 2013) and monkeys (Moelier et al., 2011; Yu et al., 2015) conducted with sensitive analytical methods that can measure endogenous versus exogenous formaldehyde DNA or protein adducts have demonstrated that inhaled exogenous formaldehyde is not systemically absorbed or reaches sites distant from the point of initial contact. In addition to these studies, the available data on the toxicokinetics of formaldehyde suggest that no significant amount of "free" formaldehyde would be transported beyond the portal of entry.

In addition to studies supporting the lack of systemic delivery of formaldehyde, anatomically accurate computational fluid dynamics (CFD) models of the rat, monkey, and human have been applied to evaluate the effects of endogenously present formaldehyde on uptake from the respiratory tract. The consideration of endogenous formaldehyde concentrations in nasal tissues did not affect flux or nasal uptake predictions at exposure concentrations > 500 parts per billion (ppb); however, reduced nasal uptake was predicted at lower exposure concentrations (Schroeter et al., 2014).

3.3.3. Data are insufficient to conclude formaldehyde is causing cytogenetic effects at distant sites

The modes of action that have been proposed in the Draft IRIS Assessment (EPA, 2010) to cause leukemogenesis rely strongly on the hypothesis that exposure to inhaled formaldehyde can result in cytogenetic effects at sites distant from the portal of entry. While the NRC (2011) noted that numerous studies have shown genotoxic effects in cells exposed *in vitro*, and a few studies have shown positive cytogenetic effects in circulating blood lymphocytes in heavily-exposed workers, they also noted that it is unlikely that these effects are relevant to a possible leukemogenic effect of formaldehyde, particularly at low exposure levels. The potential leukemogenic effect and exposure-response relationships at lower exposure levels have been comprehensively evaluated by Nielsen et al. (2013, 2017).

One key study cited in multiple agency evaluations as providing evidence of cytogenetic events in the development of leukemias is by Zhang et al. (2010a, 2010b) compared the prevalence of markers of hematopoietic function and chromosomal aneuploidy among workers occupationally exposed to formaldehyde with those of a group of unexposed workers in China. Ninety-four workers were included, with 43 workers occupationally exposed to formaldehyde and 51 workers unexposed to formaldehyde as controls. The authors reported a higher prevalence of monosomy 7 (loss of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures of CFU-GM colony cells. The authors suggested that this demonstrated that formaldehyde exposure was associated with an increase in leukemiaspecific chromosomal aneuploidy in vivo in the hematopoietic progenitor cells of the exposed workers. However, no direct in vivo metaphases had been examined in workers blood. Furthermore, this was a cross-sectional comparison of blood and cytogenetic measures between two groups, and observed differences could not be established as resulting from formaldehyde exposure or due to other overall differences between the two groups.

Two re-analyses of the underlying data from the Zhang et al. (2010a) study have been published (Gentry et al., 2013; Mundt et al., 2817). The first (Gentry et al., 2013) relied upon selected underlying data provided through a Freedom of Information Act request that included: 1) individual data on blood cell counts in both formaldehydeexposed and unexposed individuals including any data on health status of these individuals; 2) individual data on the FISH results for monosomy 7 and trisomy 8 for cultures of samples obtained from 10 formaldehyde-exposed workers and 12 unexposed controls; 3) data on additional chromosomal abnormalities examined and/or observed; and 4) details of the methods sufficient for a qualified scientist to replicate the results reported in the Zhang et al. (2010) study. The results of this reanalysis suggested that factors other than formaldehyde exposure likely contributed to the reported findings. In addition, although the authors stated in their paper that "all scorable metaphase spreads on each slide were analyzed, and a minimum of 150 cells per subject was scored," this protocol was not followed specifically for chromosome 7 or chromosome 8 (recent correspondence indicates a minimum of 150 total metaphases were scored for 24 chromosomes per subject). Far too few cells were counted to draw any meaningful conclusions, and far fewer than the approximately 400 per chromosome cited in previous analyses in which the protocol was described (Zhang et al., 2005, 2011). In addition, the assays used (CFU-GM) do not actually measure the proposed events in primitive cells involved in the development of AML. Evaluation of these data indicates that the aneuploidy measured



could not have arisen in vivo, but rather arose during in vitro culture.

In 2014, Mundt et al. requested the individual exposure measurement data for each of the participants in the Zhang et al. (2010a) study from NCI. In 2016, the request was in part granted and the mean formaldehyde estimate for each exposed worker (but not the individual exposure measurement values) was provided via a Technology Transfer Agreement (TTA) with NCI. Using these data, the Gentry et al. (2013) reanalysis was extended to include exposure-response analyses. Results of this second reanalysis showed that differences seen at the group comparison level, i.e., comparing the prevalence of white blood cell, granulocyte, platelet, and red blood cell counts at the group level in fact were independent of measured formaldehyde exposure level. Among exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of ML risk. Differences between the two groups of workers, other than formaldehyde exposure, were therefore likely to explain the results reported by Zhang et al. (2010a).

Subsequent studies of the same population of formaldehyde-exposed and non-exposed workers in China (Lan et al., 2015; Seow et al., 2015; Bassig et al., 2016) have been suggested by the authors to confirm the results of Zhang et al. (2010a); however, many of these studies report results from the same biological samples as Zhang et al. (2010a) and therefore, do not provide replication of the results. The repeated use of the original Zbang et al. (2010a) data, and its implications, have been reiterated (Pira et al., 2017; Gentry et al., 2013; Speit et al., 2010) and the original authors have responded to some of the criticisms (Rothman et al., 2017; Lan et al., 2015; Zhang et al., 2010b). Replication of the Zhang et al. (2010a) results will require replication in an independent population of formaldehyde-exposed workers, and where methodological issues are adequately addressed. An attempt to replicate the results could be conducted in the same population of workers as Zhang et al. (2010a) and Lan et al. (2015) in which the median exposures to 43 workers were 1.28 ppm (10th and 90th percentile: 0.63, 2.51 ppm). However, as noted previously (Section 3.1.1), no evidence of an association between formaldehyde exposure and leukemias has been reported in multiple recent epidemiological studies with large numbers of subjects that have been exposed to concentrations > 2.0 ppm. The increasing evidence that inhaled formaldehyde does not move beyond the portal of entry (Section 3.3.2) also calls into question many of the conclusions from Zhang et al. (2010a).

Albertini and Kaden (2016) reviewed the body of data that reportedly indicates genetic changes in circulating blood cells and in blood-borne hematopoietic precursor cells (HPCs). These changes have been considered to be indicators that systemic genotoxicity occurs after human inhalation exposure to formaldehyde, although the mechanisms by which this could occur remain unknown. For each study, the authors examined the sources of exposure, possible co-exposures, biomarkers for internal exposures and genetic signatures of formaldehyde effects.

In reviewing the available studies, many genetic changes in blood cells were noted by Albertini and Kaden (2016), with a contrast in results between animal and human studies: the majority of animal studies were negative and the majority of human studies were positive. This pattern was attributed to the difference in target cell being studied, with bone marrow cells studied in animals and peripheral blood lymphocytes studied in humans. Exposure of human cells to formaldehyde at sites of contact in vivo could provide opportunities for exposure of Tlymphocytes to formaldehyde or products of oxidative stress, which could result in the genetic changes observed in peripheral blood cells. However, these results are inconsistent with results from controlled animal studies, discussed previously, that demonstrate - by labeling administered formaldehyde - inhaled (exogenous) formaldehyde does not travel beyond the portal of entry (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011). Therefore, these types of genetic changes reported in human studies do not provide evidence that formaldehyde moves beyond the portal of entry to the bone marrow, which would be necessary to result in direct induction of chromosome-level mutations in the bone marrow. Despite the apparent inability of exogenous formaldehyde to reach the bone marrow, the mutagenic effects of formaldehyde in bone marrow have not been tested in humans.

Albertini and Kaden (2016) concluded that overall, the available literature on genetic changes following formaldehyde exposure did not provide convincing evidence that exogenous exposure, and specifically exposure by inhalation, induces mutations as a direct DNA-reactive effect at sites distant from the portal-of-entry tissue. This would include proposed mode of actions that involve a stem cell effect at the portal of entry with circulation back to the bone marrow. Such exposures have not been shown to induce mutations in the bone marrow or in any other tissues beyond the point of contact. Thus, the weight of scientific evidence does not provide biological plausibility of lymphohematopoietic cancers, as proposed by EPA (2010) and NTP (2011).

3.4. Dose-response assessment

Several NRC (2011) peer-review comments were raised regarding the dose-response assessment conducted by EPA in the Draft IRIS Assessment (2010). One comment highlighted the need to conduct independent analyses of the dose-response models, using the data from the Beane Freeman et al. (2009) study to confirm which models fit the data appropriately (NRC, 2011). Using the original data from the key study (Beane Freeman et al., 2009) and documentation provided in the Draft IRIS Assessment, Van Landingham et al. (2016) attempted to duplicate the reported inhalation unit risk (IUR) values for Hodgkin lymphoma and all leukemias and address the NRC Committee's questions regarding application of the appropriate dose-response model. Overall, there was difficulty duplicating the IURs reported by EPA (2010), largely due to a lack of critical information provided in the IRIS documentation. Perhaps most problematic, the first step of the analysis did not determine significant exposure-response relationships between formaldehyde and lymphohematopoietic endpoints for the metric (cumulative exposure) needed in the estimation of an IUR. The authors concluded that the resulting analysis, while it could be mechanically performed, provided no valid or useful insights on the risks of formaldehyde exposure. The lack of apparent exposure-response relationships for selected endpoints raises the question whether quantitative analyses are appropriate for these endpoints, and if so, how results are to be interpreted.

The NRC (2011) also noted the need to consider alternative extrapolation models for analyzing the cancer data. In 2013, Starr and Swenberg proposed a novel "bottom-up" approach for bounding lowdose human cancer risks using formaldehyde as an example (Starr and Swenberg, 2013). This approach requires information on background risk, background or endogenous exposure and the additional exogenous exposure of interest. The results of this approach provided estimates of risk ($< 3.9 \times 10^{-6}$) that were more than 14,000-fold lower than the corresponding Draft IRIS Assessment (EPA, 2010) estimate for all leukemias (5.7 \times 10⁻²) and considers the impact of background endogenous formaldehyde concentrations, which is not considered in the Draft IRIS Assessment (EPA, 2010). In 2016, Starr and Swenberg provided an update to this approach, incorporating new formaldehyde-DNA adduct data, and allowing for uncertainty in two of the parameters (background cancer risk and background endogenous concentrations of formaldehyde) (Starr and Swenberg, 2016). Consideration of the statistical uncertainty in these two parameters resulted in estimates of risk for leukemias that were even smaller than those initially estimated in Starr and Swenberg (2013). The authors concluded that these estimates provide a reality check for the IUR presented in the Draft IRIS Assessment (EPA, 2010). In addition, the large discrepancy between results using an approach that relies on molecular dosimetry data (i.e., the bottom up approach) versus one that relies upon uncertain retrospective occupational exposure reconstructions (i.e., the approach



relied upon in \mathbb{EPA} (2010) call into question the credibility of attributing increases in human mortality from leukemias to occupational exposure to formaldehyde.

3.5. Methods for evidence integration

The NRC (2011) noted that the Draft IRIS Assessment's (EPA, 2010) approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version.

Since the Draft IRIS Assessment (EPA, 2010) and the NRC (2011) peer review, several frameworks have been developed to integrate evidence across different lines of scientific inquiry including epidemiology, toxicology and mode of action studies (Adami et al., 2011; Lavelle et al., 2012; Linkov et al., 2015; Rhomberg, 2015b; Rooney et al., 2014; Woodruff and Sutton, 2014). The EPA has also proposed preliminary approaches for integrating evidence in response to the NRC (2011) peer review of formaldehyde (EPA, 2013a).

Rhomberg et al. (2011) applied a hypothesis-based weight of evidence approach to evaluate formaldehyde and leukemogenesis, considering how human, animal and mode of action results inform one another. In comparing the potential alternative proposals for causality, the authors concluded that the evidence for a causal association between formaldehyde exposure and leukemia is not only weak but strains biological plausibility (Rhomberg et al., 2011).

Nielsen et al. (2017) also considered the body of formaldehyde research while re-evaluating the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Nielsen et al. (2017) iterated that although formaldehyde is genotoxic and causes DNA adduct formation, it is also clastogenic. Exposure-response relationships from both animal and human data were nonlinear, and relevant genetic polymorphisms had not been identified. Although one epidemiological study had reported an association with nasopharyngeal cancer and others reported inconsistent associations with leukemias, relative risks were not increased below 1 ppm (mean exposures). Because inhaled formaldehyde does not pass beyond the respiratory epithelium, any direct effects are limited to portal-of-entry effects (Nielsen et al., 2017).

Other reviews and syntheses of evidence focused on epidemiological studies, and this body of literature has been most variably interpreted. In 2014, an independent National Research Council committee was charged with performing a peer review of the NTP evaluation of formaldehyde for the 12th edition of the RoC (NRC, 2014b). This NRC committee produced a new definition for "sufficient evidence" of carcinogenicity as demonstrated by two or more strong or moderately strong epidemiological studies with different study designs and populations showing associations between formaldehyde exposure and a specific cancer type. In this approach, "strong" epidemiology studies do not refer to the magnitude of the association, but relect a judgment of study quality and utility made by reviewers who considered chance, bias, and confounding as alternative explanations for the observed association and found these were not reasonable explanations. Further, "strong" epidemiology studies comprised large populations with long durations of exposure and an adequate follow up period to allow for latency, and had exposure assessments that were able to discriminate between "high" and "low" formaldehyde exposure categories. This "strength of evidence" approach contrasts with a "weight of evidence approach." Although each epidemiology study was classified as one of three categories (strong, moderately strong, or weak), this approach suggests that 2 or more strong or moderately strong studies with positive results are enough to conclude sufficient evidence of carcinogenicity exists, and discounts epidemiology and animal studies that are negative or contradictory.

Meta-analyses are often used to synthesize findings across many

epidemiology studies, identifying sources of potential heterogeneity which then can be explored in interpreting the overall evidence. In the Draft IRIS Assessment (EPA, 2010), meta-analyses conducted by several investigators were considered (Zhang et al., 2009; Collins and Lineker, 2004; Bosetti et al., 2008). Since then, two additional meta-analyses were conducted (Bachand et al., 2010; Schwilk et al., 2010). Bachand et al. (2010) excluded lower-quality studies and reported a meta-RR of 1.05 (95% CI 0.93-1.20) based on 16 cohort studies and a meta-OR of 0.99 (95% CI 0.71-1.37) based on 2 case-control studies for all leukemia, reported separately due to heterogeneity. Schwilk et al. (2010) published a meta-analysis of the epidemiological findings on myeloid leukemia, but limited to the highest-exposed sub-group reported in four studies (three cohort and one case-control): RR = 2.47; 95% CI, 1.42 to 4.27. Checkoway et al. (2012) conducted a critical review and synthesis of the epidemiological evidence and concluded that results from epidemiological studies were not consistent and did not show strong results or exposure-response associations. None of these reviews, however, included the results from the extended follow up of the NIOSH garment workers study (Meyers et al., 2013), the extended follow up of the UK producers and users (Coggon et al., 2014) or the extended analyses of the NCI cohort (Checkoway et al., 2015). In addition, metaanalyses and/or critical reviews of epidemiological literature require further integration with other lines of evidence.

4. Conclusions

It has been seven years since the release of the Draft IRIS Toxicological Review of Formaldehyde (EPA, 2010). In peer-reviewing this draft report, an NRC Committee raised many substantive questions related specifically to the conclusions drawn in the document and the quantitative estimates of potential toxicity (NRC, 2011). This Committee was tasked with reviewing and commenting on information provided in the draft assessment, and did not independently conduct a review of the primary literature, but did determine that many of EPA's conclusions were not supported by the information and studies cited in the draft assessment. The committee also identified general methodologic problems with the Draft IRIS Assessment, and provided specific comments related to the evaluation of specific studies and conclusions based on the available evidence. The comments related to a causal association between formaldehyde exposure and LHM largely involved the interpretation of the available evidence at that time and the framework in which it was evaluated by EPA (2010). The committee found that EPA's preliminary conclusion that formaldehyde causes leukemia, ML or related hematopoietic cancers appeared to be "subjective' in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The absence of such a framework was judged by the committee as troublesome, given that the scientific evidence on the question was weak (NRC, 2011).

Since the NRC (2011) peer review, significant additional scientific evidence has become available that addresses many of the questions raised by the NRC Committee regarding a causal association between formaldehyde exposure and LHM. Some of these new studies and analyses were conducted in response to the NRC (2011) comments and recommendations, while others reflect ongoing work and updates of studies on this topic. All add to the scientific evidence surrounding the potential causal relationship between formaldehyde inhalation exposure and LHM, and should be addressed in the critical evaluations and integration of evidence presented in an updated IRIS Assessment.

Also since the NRC (2011) peer review, the EPA has proposed enhancements to the IRIS process (EPA, 2013b) that incorporate many of the general recommendations made by the NRC (2011) related to methodological issues. This process involves the evaluation and synthesis of evidence within separate streams of evidence (human, animal and mechanistic). However, in a critical review of the process conducted by a separate NRC Committee, while there was improvement in guidelines for evaluation and synthesis of evidence within an



evidence stream, the NRC Committee still noted limitations in synthesizing or integrating evidence across streams or categories (NRC, 2014a).

Nearly all of the recently available evidence from multiple lines of evidence, especially those studies that have been focused on addressing comments from the NRC Committee reviewing the Draft IRIS Assessment (NRC, 2011), have increased the weight of evidence favoring a conclusion of a lack of a causal association between formaldehyde exposure and LHM. The Checkoway et al. (2015) re-analysis using the data from the Beane Freeman et al. (2009) study was able to address directly several questions and comments from the NRC (2011) Committee, as the Draft IRIS Assessment (2010) was highly dependent on this study for drawing both qualitative and quantitative conclusions related to formaldehyde leukemogenicity and risk of LHM following inhalation exposure to formaldehyde. The Checkoway et al. (2015) reanalysis provides several results and insights relevant for assessing the risk of specific LHM. Not the least of these, the AML-specific results provide no support for the conclusion that formaldehyde causes AML. Associations seen between formaldehyde exposure and Hodgkin lymphoma and CML are inconsistent with other studies and also lack a plausible biological mechanism (Checkoway et al., 2015). NTP (2011) also noted that because the evidence for Hodgkin lymphoma is mainly limited to the NCI cohort study, a causal association cannot be established. No other LHM was associated with either cumulative or peak formaldehyde exposure. These results of the fuller analysis of the data from Beane Freeman et al. (2009) are consistent with recent epidemiological studies (Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014) which report no significant increase in LHM, specifically AML, among cohorts of workers exposed to formaldehyde.

The available animal evidence did not support a causal association between formaldehyde exposure and LHM at the time the Draft IRIS Assessment (EPA, 2010) was released. Since that time, additional studies have been conducted by the NTP using two sensitive assays in mice genetically predisposed to develop cancer following short-term exposure to a chemical (Morgan et al., 2017). These studies provided no evidence of changes in endpoints related to LHM or the presence of any LHM following exposure to high concentrations (15 ppm) of formaldehyde.

Studies conducted to evaluate potential mechanisms associated with formaldehyde exposure and LHM have demonstrated a lack of evidence for exogenous formaldehyde to move beyond the portal of entry. Multiple studies conducted in multiple species using highly sensitive techniques (Edrissi et al., 2013; Lu et al., 2011; Moelier et al., 2011; Yu et al., 2015) have demonstrated that while endogenous formaldehyde is present in all tissues, exogenous formaldehyde following inhalation exposure is not transported systemically. While some mechanisms for the development of LHM following inhalation exposure to formaldehyde have been hypothesized (EPA, 2010; Zbang et al., 2009, 2010a), there is no evidence to support these proposed mechanisms and the NRC Committee noted that:

"Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures." (NRC, 2011; page 45)

The more recent research all but confirms this. Several modes of action have been proposed, relying primarily on data reported by Zhang et al. (2010a) as well as subsequent evaluations of the same population of Chinese workers (Bassig et al., 2016; Lan et al., 2015; Seow et al., 2015). These include a mode of action in which risk of ML is increased due to immune suppression resulting from formaldehyde exposure (Bassig et al., 2016; Seow et al., 2015). The speculated modes of action,

however, assume systemic delivery of formaldehyde except one, which is a hypothesized mode of action in which hematopoietic cells in the nasal epithelium that are impacted by exposure to formaldehyde return to the bone marrow. The NRC Committee considered this proposed mode of action and concluded that:

"As a result, EPA could only speculate that circulating hematopoietic stem cells that percolate through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for mutations and clastogenic effects that eventually result in lymphohemotopoietic cancers. Experimental evidence of [this] mechanism is lacking." (NRC, 2011; page 45)

This currently leaves no acceptable proposed mode of action for the development of LHM following inhalation exposure to formaldehyde that can be scientifically substantiated.

The available toxicokinetic data also do not support the transport of inhaled formaldehyde from the portal of entry. The studies by Swenberg and colleagues unequivocally demonstrate that exogenous formaldehyde exposure does not increase formaldehyde concentrations measured in any internal tissues over those in unexposed animals, i.e., endogenously produced formaldehyde is the predominant if not only source of internal formaldehyde (Edrissi et al., 2013; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011; Yu et al., 2015).

The biological plausibility of a mode of action for the development of LHM following inhalation exposure to formaldehyde has relied heavily upon the incompletely reported results from the Zhang et al. (2010a) study in which the authors report differences between groups of formaldehyde exposed and unexposed groups in the frequency of monosomy 7 (loss of chromosome) and trisomy 8 (gain of chromosome), based on metaphase spreads prepared from culture of CFU-GM colony cells. However, reanalysis of the underlying raw data in two studies (Gentry et al., 2013; Mundt et al., 2017) have identified methodological problems with this study that challenge these conclusions, as well as demonstrate a lack of association between level of formaldehyde exposure and the observed aneuploidy (or any of the haematological measures).

Overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of LHM has increased substantially since the completion of the Draft IRIS Assessment (EPA, 2010) and release of the NRC peer review (NRC, 2011). New evidence has been published in each of the major streams of evidence (i.e., human, animal and mechanistic) that consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the NRC (2011) scientific criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure. Regardless of which of the several similar approaches to integrating the available evidence between formaldehyde inhalation exposure and the potential for leukemia risk, there is at most only limited suggestive positive evidence, in contrast with the bulk of evidence suggesting no such association. Therefore, a conclusion of causation is not justified scientifically. The scientific landscape into which EPA will release its long-anticipated revised IRIS Toxicological Review of Formaldehyde - Inhalation Assessment is very different from that of the 2010 Draft IRIS Assessment, both in terms of improved methodological approaches and the available epidemiological, toxicological and mechanistic evidence. Given formaldehyde's commercial importance, ubiquity in the environment and endogenous production, accurate determination of whether occupational, residential, or consumer exposure to formaldehyde causes leukemia or any type of human neoplasm is critical.



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Updates from ORD National Center for Environmental Assessment (NCEA) & Integrated Risk Information System (IRIS)

Tina Bahadori, NCEA Director Kris Thayer, NCEA IRIS Division Director

Briefing for the STPC September 20, 2017





National Academy of Sciences (2014) Overarching Statements

2014



- "Overall, the committee finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time, and the present committee's recommendations should be seen as building on the progress that EPA has already made." [p.9]
- "... the IRIS program has moved forward steadily in planning for and implementing changes in each element of the assessment process. The committee is confident that there is an institutional commitment to completing the revisions of the process... Overall the committee expects that EPA will complete its planned revisions in a timely way and that the revisions will transform the IRIS Program." [p.135]





Appropriations Language

- Report 114-281 Committee on Appropriations (June 16, 2016)
 S.3068 Department of the Interior, Environment, and Related Agencies Appropriations Act, 2017
- https://www.congress.gov/114/crpt/srpt281/CRPT-114srpt281.pdf
- IRIS (p. 63)
 - ✓ EPA to convene an interagency working group of relevant executive branch stakeholders and co-chaired with OIRA
 - √ Review compliance with NAS recommendations (2014)
 - Transition from single point estimates of hazard and exposure to distribution of estimated hazards, exposures, and risks, including central tendency values
 - o Processes for evaluating study quality, relevance and risk of bias
 - o Use of transparent and reproducible weight-of-evidence process
 - o Selection of an adverse outcome
 - \circ Use of default linear low-dose extrapolation and other default modeling approaches
 - Timetable for EPA's full implementation of NAS recommendations for all IRIS assessments
 - o Report within 180 days





The IRIS Interagency Workgroup (IWG)

- IWG was convened in August 2017
- Co-chaired by EPA/ORD and OMB/OIRA Richard Yamada overseeing.
 - Membership from across the federal family
- Has met twice and has a third meeting scheduled for the 25th of September.
- A brief Report to Congress (on the order of 2-3 pages) will be drafted, where we will summarize the meetings and actions, and plans moving forward.
- In addition, NCEA has requested the National Academies to hold a public meeting to evaluate IRIS's progress and to issue a consensus report within 6 months of that meeting. That report will also inform the IWG.





Broader Engagement

• SAB

- SAB Briefing, August 30, 2017
 - SAB letter to the Administrator about IRIS:
 https://yosemite.epa.gov/sab/sabproduct.nsf/0/A9A9ACCE42B6AA0E8525818E004CC597/\$File/EPA-SAB-17-008.pdf
 - "The SAB has observed significant enhancements in the IRIS program over the past few years, with impactful changes over the past year, and marked progress over the past six months."
 - "The changes are so extensive and positive that they constitute a virtual reinvention of IRIS."
 - "The SAB notes that no other federal entity performs the IRIS functions, and that IRIS helps ensure consistency in chemical assessments within the Agency and across the federal government."
- SAB Chemical Assessment Advisory Committee (SAB-CAAC) briefing scheduled for September 27-28, 2017
- Congressional hearing
- NAS
 - Agreement in place to peer review formaldehyde (Congressional requirement)
 - (possibly) arsenic
- Stakeholder outreach
 - Systematic review communities
 - Requests for correction





IRIS Multi-Year Agenda

Developing Agenda	Group	Chemicals		
 Released to the public 		Manganese		
December 2015		Mercury/methylmercury		
 Survey EPA program and regional offices for their 	1	Nitrate/nitrite		
assessment needs		Perfluoroalkyl compounds		
 Estimate the resources needed for each 		Vanadium and compounds		
assessment by science	2	Acetaldehyde		
discipline		Ammonia (oral)		
 Discuss with senior EPA officials how to meet the 		Cadmium and compounds		
most high-priority needs		Uranium		
 Allocation of IRIS resources based on the 		Di-(2-ethylhexyl) phthalate		
plan		Dichlorobenzene isomers		
Evaluate annually for	3	Methyl t-butyl ether (MTBE)		
continued relevance		Nickel and compounds		
		Styrene		





How is IRIS Focusing?

Increase transparency and full implementation of systematic review

 implement using approaches that foster consistency across the IRIS program; many active and all new starts address ALL SR-related recommendations of 2014 NRC report

Modernize the IRIS Program

 through automation and machine learning to expedite systematic review, incorporation of emerging data types

Modularize product lines

implement a portfolio of chemical evaluation products that optimize the application of the
best available science and technology. These products will allow IRIS to remain flexible and
responsive to clients within the EPA as well the diverse collection of stakeholders beyond
EPA, including states, tribal nations, and other federal agencies.

Enhance accessibility

 provide outreach and training to make systematic review practices ubiquitous and more accessible; enhance data sharing through publicly available software platforms for assessments developed by EPA, other federal and state agencies, industry, academia and other third-parties.





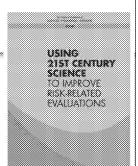
Other IRIS Improvements

Next Generation IRIS

- IRIS in the 21st Century implement recommendations of the NAS 2017 report, Using 21st Century Science to Improve Risk-Related Evaluations;
- Collaborate with EPA's National Center for Computational Toxicology (NCCT) to build expert-judgement case studies that inform assessment development and fill gaps in assessments, especially for data poor chemicals; inform where resources should be strategically invested to generate additional data.

Improved Management Practices

- Create efficiencies engage other agencies to share common practices, data, and tools, and more efficiently leverage resources across the federal government.
- Improve timeliness and responsiveness deploy program and project management tools to more effectively and efficiently utilize human resources to ensure timely delivery of products.







Systematic Review



ess ,2

A structured and documented process for transparent literature review^{1,2}

"... systematic review is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent"

¹ Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. EPA-HQ-OPPT-2016-0654. https://www.epa.gov/sites/production/files/2017-06/documents/prepubcopy_tsca_riskeval_final_rule_2017-06-22.pdf



² Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011



NAS (2017): Reflections and Lessons Learned from the Systematic Review



APPLICATION OF SYSTEMATED REVIEW METRICS WAS OVERALLS TRAINED FOR EVIDANCE OF THE TRAINED TO THE STREET OF THE CHARGAIL

- "...one disadvantage in conducting a systematic review is that it can be time and resource intensive, particularly for individuals that have not previously conducted a systematic review." [p.157]
- "The committee discussed at length whether it could provide EPA with advice about when a systematic review should be performed but decided it could not be more specific because that decision will depend on the availability of data and resources, the anticipated actions, the time frame for decision making, and other factors." [p.157]
- "The committee also recognized that it might be advantageous for EPA to build on existing systematic reviews that are published in the peer-reviewed literature." [p.157]
- "The committee recognizes that the methods and role of systematic review and meta-analysis in toxicology are evolving rapidly and EPA will need to stay abreast of these developments, strive for transparency, and use appropriate methods to address its questions." [p.157]





Making Systematic Review Pragmatic and Feasible For IRIS

- Standard operating procedures (IRIS Handbook) and chemical-specific protocols
- Use of specialized software applications and automation
- Targeted focus, especially for evidence-rich topics
 - Make better use of well-conducted existing assessments as starting point
- Multiple assessment products ("modularity")
- Solicit early feedback during scoping and problem formulation via assessment plans
 - Summary of scoping and initial problem formulation conclusions, objectives and specific aims of the assessment, draft PECO (Population, Exposure, Comparators, and Outcomes) framework that outlines the evidence considered most pertinent to the assessment, and identification of key areas of scientific complexity
- Utilize iterative protocols to ensure focus on best-available and mostinformative evidence as the assessment progresses

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Protocol: Literature Searching and Screening

4. LITERATURE SEARCH AND SCREENING **STRATEGIES**

basic practices

4.1. USE OF EXISTING ASSESSMENTS

Bescribe any use of existing assessments that serve as starting points for the literature

special topics

4.2. LITERATURE SEARCH STRATEGIES

Literature search strategies were developed using key terms and words relate -22relevant search terms through [1] reviewing PubMed's Medical Subject Headings [26 24 relevant and appropriate terms (2) extraoring humans. previously identified primary data studies that are known to be relevant to the topol

wolf 7 4.4. SCREENING PROCESS Studies that dumply with the criteria specified in the PECO inclusion while those that do not meet these criteria will be exclude: 10 the exclusion criteria noted below will be applied. However, the refer will be reviewed to identify PECO-relevant studies that may have been it 17

- Records that do not contain original data, such as reviews, editorials.
- R is possible that inspublished data directly relevant to the PECO statement may be identified during the course of the essessment, in this case, EPA is able to obtain external peer review of the corners of the data are wilking to have the body detack and resids made publishy accessible. The peer review would include an evaluation of the study similar to that for peer review of a journal publication. The EPA would identify and select two to three scientists knowledgeable in scientific 14 4.4.1. Multiple publications of the same data

IRIS only included publicly accessible, peer-reciewed information in its evaluations. How

subgroups, additional outcomes or expositres outside the scope of an evaluation, or longer follow-up) can be identified by examining suffice affiliations, study designs, colors name, enrollment criteria, and enrollment dates. If necessary, study authors will be contacted to clarify any uscertainty about the independence of two or more articles. IRIS will include all publications on the 20 study, selectione study to use as the primary, and consider the others as secondary publications Studies that have not been peer-reviewed (e.g., conference abstracts)
 with annotation as being related to the primary record during data abstraction. The primary study

Multiple publications with overlapping data for the same study (e.g., publications reporting

. {others decided by the assessment team}

Studies will be screened for inclusion using a structured form in flist the software and lication and $\rm SSI$ in needs of site, e.g. DistillerSR (Existence Partners,

theses/dissertations, working papers from research groups or committees, and white



Protocol: Study Evaluation (Epidemiology)

6.2. EPIDEMIOLOGY STUDY EVALUATION

Evaluation of epidemiology studies to assess bias and study sensitivity will be conducted for the following domains: exposure measures, outcome measures, participant selection, potential

confounding analysis, selection of reported results, and study sensitivity (Table 2)

Table 2. Domaius of evaluation for epidemiology studies

Domain	Example information
Exposure measures	Source(s) of exposure (consumer products, occupational, an industrial accident) and a exposure data, bisoding to automie, level of detail for job history data, when measure were taken, type of biomerrien(s), assay information, reliability data from repeat mea- sticides, violations studies.
Outrone	Source of participie (effect) measure, blinding to exposure status or level, how measured/classified, incident versus prevalent disease, evidence from velidation studies revealence (or distribution summerly statustics for community measures).
Participant selection	Study design, where and solen was the musy conducted, and who was excluded? See process, exclusion and inclusion ordinals, type of controls total eligible, comparison by participants and comparticipants for tollowed and not followed, Snei analysis group study include potential womerable/susceptible groups or Restager?
Patential confounding	Background research on key confounders for specific populations or settings; particip characteristic data, by group; private graphs for consideration of potential confo- strength of associations between exposure and potential confounders and between confounders and outcome, degree of exposure to the confounder in the population.
Analysis	Extent (and if applicable, treatment) of missing data for expassors, curroms, and configuration to modeling, classification of expassors and ourcome variables (continuous categories), testing of assumptions, cample size for specific analyses, relevant sensitionaryses.
Selective reporting	Are results presented with adequate detail for all of the endocions of interest? Are no presented for the full sample as well as for specified subgroups? Were stratified area modification; motivated by a specific hypothesis?
Sensitivity	When expressive range is spanned in this study? What are the ages of perticipance (e.g. young in studies of published developments? What is the length of follow-up find reuta long latency gentrally? Obtained referred groups and the letter of proposers continued groups (i.e., the extent it which the "unexposed group" is truly unexposed, and the of disposure in the group designated as "exposed".

Table 5. Example question specification for evaluation of domains in epidemiology studies

Core question	Example prompting questions	Example follow-up questions		
legative Does the exposure in a serier reliabily facilities in a few end of exposure in a serier of the exposure i	For all: Ones the exposure measure coption the major source(pi of variability) in apposar wrong the participants, considering intensity. Problemon, and other of response. Ones the exposure measures reflect a reviewer time vindeout? For can the revisionable problemon resource in the time and the reviewer time vindeout? And to the revisionable problemon resource must be time and the reviewer dishouncement of the problemon resourcement Reflet) to the Effect of the sectioning or the causant Reflet to the presence of the suddome (S. a., reverse causality). For case-control sudden of recognitions a response.	moderate, is there en edequate statistical approach		
	Se exposure based or a comprehensive part follow position, stating, with registry, time period, and use of specific materials? For biomarkers of exposure, general peopletion: Su observations of exposure, which are the intra-lens intervasion predictions of the properties of the properties of the sample of the stating to be affected by procramations? As whose loss hard the lenst of forest loss deat with adequately. What is exposure from-period is reflected by the biomarker? If the half-life is show, what is the correlations between coroal pressurements of exposure. In additional properties of the correlations between coroal pressurements of exposures.	potential for thes, what is the predicted threation or predicted threation or distortion of the bias on the effect estimate (if there is enough latermentian)?		
Patrome Jose the occurring Jose the occurring Joseph Male Joseph M	For all: It disease accentenement having to be affected by knowledge of or presence of the above rather special access to health care, if leave on such reported history of diseases on bealth care, if leaves on such reported history of diseases. For case accentral studies issue conditionable diseases acceptance of the above rather and acceptance of the acceptance of t	is there a concern that any possession in the parameters of the non-differential, differential, or both? What is the predicted direction or discorder of the bear on the effect settlement (if there is enough information)?		
	For mortsifity measures: • How well does cause of death data reflect accordance of the disease in an includual? How, well do mortsifity data reflect incidence of the disease?			

For diagnosts of disease measures:

* Is diagnosts based on standard dinical orders? If head on standard dinical orders? If head on standard dinical orders?

The principles and framework used for the evaluation of epidemiology studies are baseds Cockrane Risk of Bise in Non-randomized Studies (RCBINS) of interventions (ROBINS-I) 31,3016) but modified to address environmental and occupational exposures. The under

philosophy of ROBINS-1 is to describes attributes of an "ideal" study with respect to each a evaluation domains (e.g., exposure measurement outcome classification, etc.). Core and grounding methods are used to callect information to study evaluation of each domain. In addition, excerted





Protocol: Study Evaluation (Animal)

n	aformation ecassory for study valuation	deficient if not reported ") * Species; tests entitle debt enopoints investigated important investigated important information, which also beautiest prostation secondary inhalp based on the needs of a given assistant and an enopoint in the prostation.	Domain	Metric						
		enopoints investigated) Important information, which sti- brackets contain secondary inhall based on the needs of a given ass	Domain	Metric						
		Important information, which set brackets contain secondary inhor based on the needs of a given ass			Criteria			→ 1		
		based on the needs of a given as:			weight class in many services a contaminate using computer shives systems (e.g., as a single class in many behaviors assessments). on the case in many behaviors assessments in the contaminate of the contaminate of the contaminate of the contaminate assessments.					
				Control for						
		sylographics. (3)	78	variables across	the common and for any consistent across exper	********				
			٤.	experimental	additional variables, introduced intentionally	Domaio		Criteria		
		 Test extinsi – strain; est (e.g., trousing, feed, ma) 	E.	Brochs	mitigated by knowledge or inferences regard		Sensitivity and	Collection Control of the control o		
		ge.g., mousing, reed, mag procedures); age or book	100		which the variable can influence the endpoin	1	specificity of the endpoint	for, or the finding of, the antiposite equivations. Second on the endpoint evaluation protocol usest for the endpoints of interest		
		Expanse merhads – text	-E		A very important example to consider is who		evaluations	specific considerations will oppically include		
		route of administrations	ng/Variabie		controlled to attribute the effects of exposure sions. Generally, well-conducted exposures:	1		Concerns regarding the sensitivity of the specific protocols for		
		volume, exposure chard	£.		exposures and will include experimental cost			evaluating the endpoint of interest (i.e. assays can differ dramatically in		
>		verification methods)	20		confounding (e.g., use of a suitable vehicle of			terms of their ability to detect effacts), and/or their timing (i.e. the age of anima's at assessment can be critical to the appropriateness and		
ğ		Experimental design—(8)	Seafers		Other examples of variables that may be unit			sensitivity of the evaluation). This includes both overestimates on		
준		during exposure and etc. systemton(s) (e.g., isoso	8		experimental groups include: protective or to			underestimates of the true effect, as well as a much higher (or lower)		
ž		■ Endocint evolutations → c			exacements effects; that composition; surgical			probability for detecting the effect(s) being assessed.		
Reporting Quality		were measured, process		Lack of selective	in a good study, information is reported on a			Concerns regarding the specificity and salidity of the protocols. This		
ě		and negative controls.	Actistion	deta raporting and	comparisons for all animals, across treatment			includes the use of appropriate protocol controls to rule out non- specific affects, which can often be inferred from established guidelines		
		rapido of bissue/ organije	ž.	uneccounted for	Aspects to consider include whether all shall			ov historical essay data. It may be considered useful for insensitive		
		(e.g., surgery, co-treat)	* ,	less of anomais	results (if not, are explanations, such as deal) gravided), and whether expected comparable			conspiler, or novel protocols to include positive and/or negative		
		 Results presentation – to were investigated inhorit 	S 55		from the analyses, in some studies, the public	85		controls.		
		were investigaced, most assessed, semple size, of	22		(e.g., a soite of standard measures in a guide	Residts Display		Concerns regarding adequate sampling. This includes both the appearmental unit (e.g., fitter; animal) and endpoint (e.g., number of the control of the		
		maternal toxicity in deed	§.		Note: This metaic does not address whether:	ă S		atides evaluated). This is typically interned from historical knowledge of		
		in long-term bicannays	æ		considers statistical test methods.	1 96		the assay or comparable assays.		
		Although such decisions should			Consider whether there are notable issues to	Measures and Re		Notes: Numer relevance of the endpoint is not addressed during study		
		ericrosotion is not reported, it is authors. However, for other mist		Charactarisation of the exposure to the	of the exposure levels, or of exposure to the			evaluation; for under sampling without blinding (e.g., sampling bles), this with typically laud to grace overestimates of effect; seemble size is generally not a		
				compound of	on the chemical being assessed, this may ing			reson for exclusion.		
		confidence condusions if it they but to study authors.		interest:	stephity and composition (e.g., punity; some	8	Usability are	Consider whether the results are analysed or presented in a way that times		
		Note: Studies adhering to BLP (g)			exposure generation and analytic verification	2	transparency of the	concerns regarding the reliability of the findings.		
		established by (interjustions) ago	20		tained levals and spacing between exposure	Dogere	gressrited data	frams that suit sypically se important to consider include:		
		quality	sitivity		methods); and details of exposure methods?	18		Concern that the lavel of detail provided itees not above for an informed leterpresention of the results by guarafeest conductors without.		
	Docarion of	loeally, animal studies are rando	S S S		gavage volume), in some cases, exposure bid	1 "		quentitative data; discussing neoplesms without distinguishing between		
ž 3	namers for	chance of being assigned to any	8		trasted animals can morgate concerns regard	1		trenign and matigned survices; our presenting reurability;		
8 8	sperimental	alfocation procedures sufficiently	(Nethods		on the validity of the biomarker for the ches	1		Concern that the way in which the data were analyzed, compared, or		
S =	:oups	ov good, are studies indicating to exposure, for example eccording	12		Note: White this identifies uncertainties in dis salid reason for exclusion from Wezerd D	1		cresented is inexpropriate or misleading. Examples include: failing to control for litter effects (e.g., when presenting out date rather than the		
Š		of randomization. The least creds	\$	Litility of the	Based on the known or oresumed thotosiciti-	1		control for littler effects (e.g., when presenting pup date rather than the preferred littler date), pooling reserving hom males and females or ecross		
ž.		how groups were assigned.	5	exposure design for	evaluated, consider whether there are notati	1		lesion types: failing to scioress observed or presumed toxicity (e.g., in		
2 8	Riading of	Good studies will conceal the 196	6 the endoors of onterest	frequency, or duration of exposure. For exect	'		assessed animals: in carns) when exposure levers are known or expected			
ğ ir	vestigatore,	the endpoint evaluations (and, a)		will cover a greater proportion of the develop-	1		to be Nighly took; incomplete presentation of the data (e.g., presenting			
S 2	articularly during	personnel and technicians). Cons			critical to the system of interest, while petter	1		continuous catales dichotomiced); or non-preferred display of results (e.g., using a different resocut than is expected for that assay). The		
	LIST NE	outcome measures are more obje-			other chronic outcomes will be of longer dut	1		evaluator should support have or why, and to what extent, this might		
	ssecurent.				infrequently or sporadically, or, convensely of	1		misread interpretations.		
				L	depending on the evolution level, can impaid	1		Aicter: Concerns regarding the statistical methods spalled are not addressed during study evaluation, but should be flagged for review by a statistician.		





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Protocol: Study Evaluation (General Approach)

6.1. STUDY EVALUATION OVERVIEW

The general approach (described in this section) of study evaluation for epidemiology and animal studies is the same, but the specifics of applying the approach differ and thus they are described separately in the following sections (Sections 6.2 and 6.3)

The evaluation will be conducted independently by at least two review 5 for comparing and resolving differences. For studies that examine more than 5 cutcome, the evaluation process will be outcome or endpoint-specific, as the 6 vary for the different endpoints.

For each study (specifically, as outcome or group of related outcomes 3 study or in a sample within a study), in each domain, reviewers will reach a co 10 Good. Adequate, Poor, or Critically Deficient. It is important to stress that \$11 performed in the context of the study suitity for hazard identification of inds. 12 While limitations specific to the usability of the study for dose-response analyst to inform those later decisions), they do not contribute to the study confidence in the study confidence in the study confidence in the study of the study of the study of the study of the study confidence in the study of the

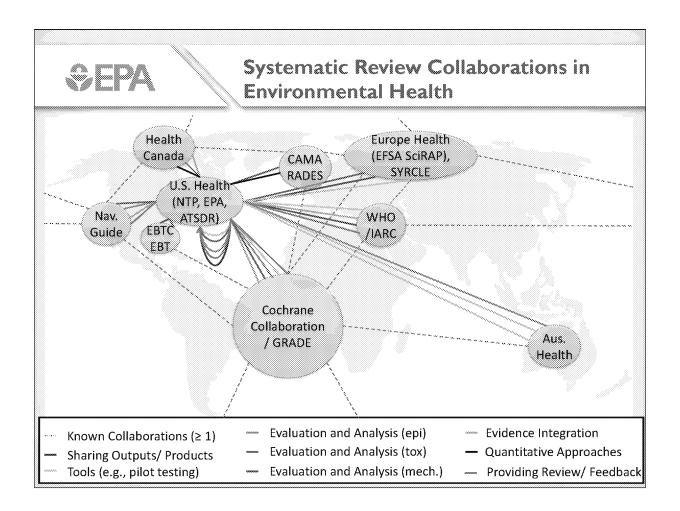
- "Good" is intended to represent a judgment that there was appropriate;?
 relating to the domain, and any minor deficiencies that were noted with to influence the study results.
- "Adequate" indicates a judgment that there were experimental limited. ²⁶ domain, but that those limitations are not likely to be severe or to have ²¹ on the results.
- "Poor" denotes identified biases or deficiencies that are interpreted at 24 aubstantial impact on the results or which prevent reliable interpretad findings.
- "Not reported" indicates that the information necessary to evaluate the 27 judgmen was not available in the study. Generally, this term carries the same fig. 28 is a robust interpretation as "Poor" for the purposes of the study confidence class. 25 limitation on the number and severity of other limitations identified in the study it may are may not use.
- worth reaching out to the study authors for this information (see discussion below).

 "Critically Deficient" reflects a judgment that the experimental conduct relating to the domain question introduced a flaw so serious that the study should not be used without

Once the evaluation domains have been considered, the identified strengths and limitations will be combined to reach a study confidence classification of High. Medium. Low. or Uninformative. This classification will be fossed on the reviewer integements across the evaluation domains, and will include consideration of the fillely impact of the stored deficiencies in bias and sensitivity, or inadequate reporting, on the results. The classifications, which reflect a consensus judgment between reviewers, are defined as follows:

- High Confidence: No notable deficiencies or concerns were identified the potential for bias is unlikely or siminal, and the study used sensitive methodology, in general, although classifications are not decided by "corong", high confidence studies would reflect judgments of good access all or most evaluation domains.
- Medium Confidence: Possible deficiencies or concerns were noted, but the limitations are
 mailely to be of a substantive degree. Generally, medium confidence studies will include
 adequate or good judgments across most domains, with the impact of any identified
 limitation not being judged as severe.
- Low Confidence: Deficiencies or concerns were noted, and the potential for substantive
 bias or analoguate sensitivity could have a significant import on the study results or their
 interpretation. Typically, flow confidence studies would have a poor evaluation for one or
 more domains (unless the impact of the particular limitations on the results is judged as
 matikely to be severe).
- Uninformative: Serious flaw(a) make the study results unusable for informing hazard identification. Studies with critical delicitencies in any evaluation domain will almost always be classified as uninformative (see explanation alove). Studies with multiple poor judgments across domains may also be considered uninformative, particularly when there is a robust database of studies on the outcome(a) of interest or when the impact of the limitations is viewed as severe.





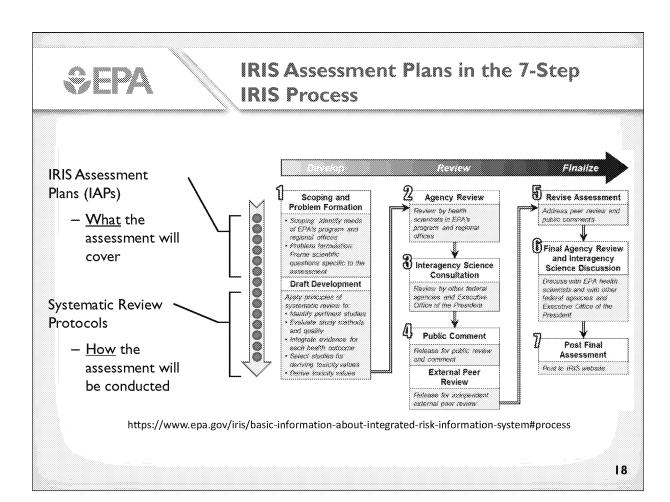




IRIS Assessment Plan Outline

- How the IRIS Assessment Plans (IAPs) fit into the 7-Step IRIS process for developing human health assessments
- Increased development and transparency of systematic review materials, including scoping & problem formulation materials
- IAPs: what they are intended to be, and what they are not
- Application of IAPs in the creation of later systematic review materials to support draft development









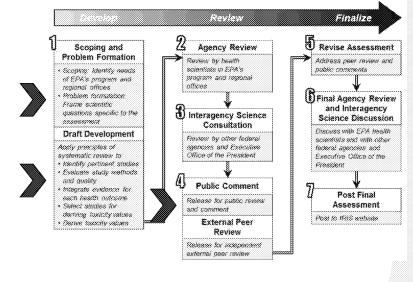
Transparency in the IRIS Assessment Process

Assessment materials will be made available for public comment at various stages in development

- Early Step 1: IRIS Assessment Plans (IAPs)
 - For ethylbenzene, nitrate/nitrite, and chloroform
 - The federal docket for public comment is open:

[TBD ~ 09/11 - 10/10]

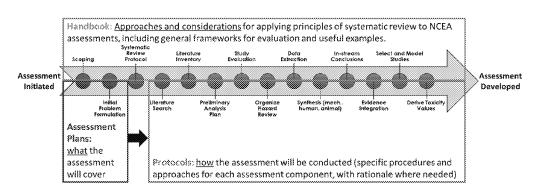
- Mid-Step 1: Systematic Review Protocols
- Step 4: Public Discussion
 Assessment Draft







Assessment Plans and Protocols in the Drafting Process

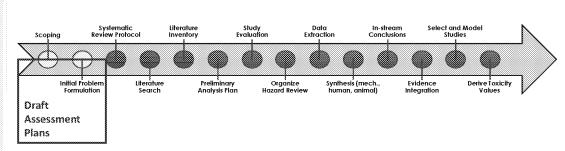


- Assessment development illustrated as sequential steps in the systematic review process, which will
 promote consistency and transparency across the IRIS program products
- General standard operating procedures will be described in the IRIS Program Handbook, while detailed approaches tailored to each assessment are described in the chemical-assessment specific plans and protocols





Role of Draft IRIS Assessment Plans (IAPs)



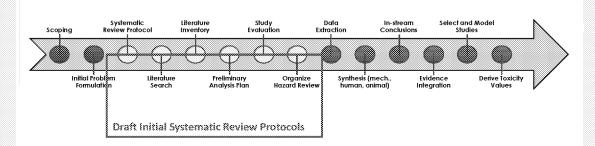
- As the INITIAL step in problem formulation, IAPs summarize:
 - Scoping and initial problem formulation conclusions
 - Objectives, and specific aims
 - Draft PECO (Population, Exposure, Comparators, and Outcomes) framework
 - Identification of key areas of scientific complexity

21





IAPs Become the Foundation for the Systematic Review Protocols



- The initial systematic review protocol will be made publicly available after review of draft IAPs
 - Protocol details how the work described in the IAP will be conducted
 - Also captures changes to IAP in response to comments received
- Protocol is iterative; the focus will be on the best available and most informative evidence
 - Public science sessions may be needed to address complex scientific issues, and refine the protocol

22





Draft IAPs Presented as Case Studies

Ethylbenzene

- RfC and RfD on IRIS (from 1991, 1987)
- Modular approach due to different levels-of-effort needed, may derive noncancer RfC, RfD, and cancer values sequentially and separately

Nitrates/Nitrites (NO₃-/NO₂-)

- RfD on IRIS (from 1991, 1987)
- Focusing on oral exposure will attempt to derive separate noncancer RfDs for NO_3 and NO_2 -, and conduct cancer assessment

Chloroform

- RfD, cancer mode-of-action (MOA) on IRIS (from 2001); IUR on IRIS (from 1987)
- Focusing on inhalation exposure will attempt to derive an noncancer RfC based upon inhalation data, and determine if RfC is protective against cancer (based upon 2001 MOA)

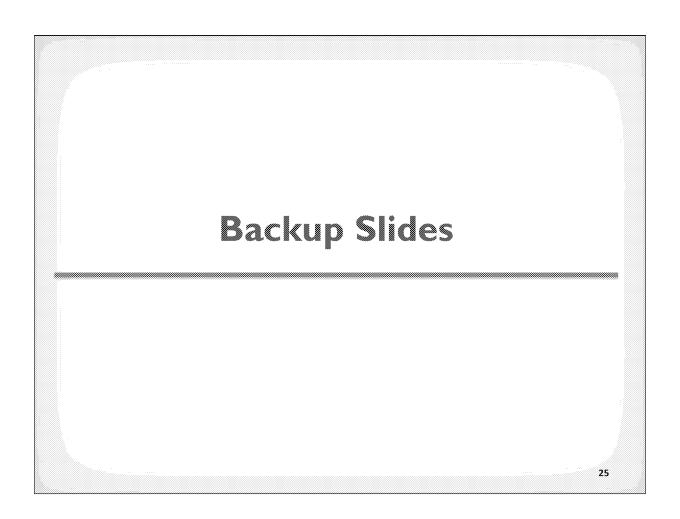
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May be questions on why ethylbenzene is being presented as scoping and problem formulation materials again; confirming that Agency need exists and that it matches EPA priorities.

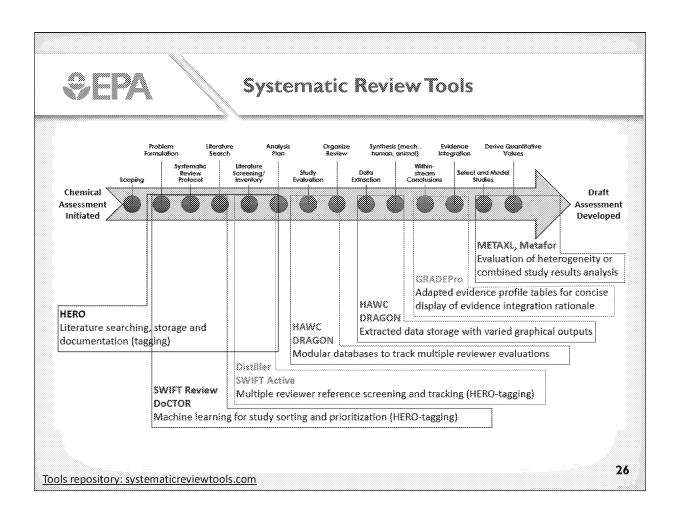




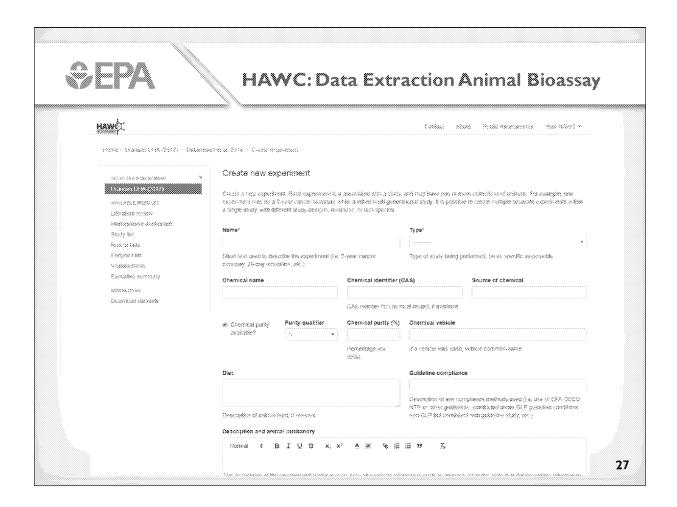




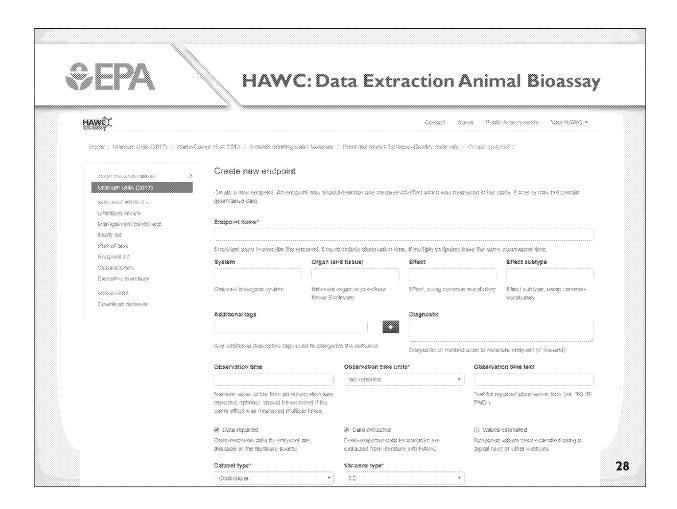




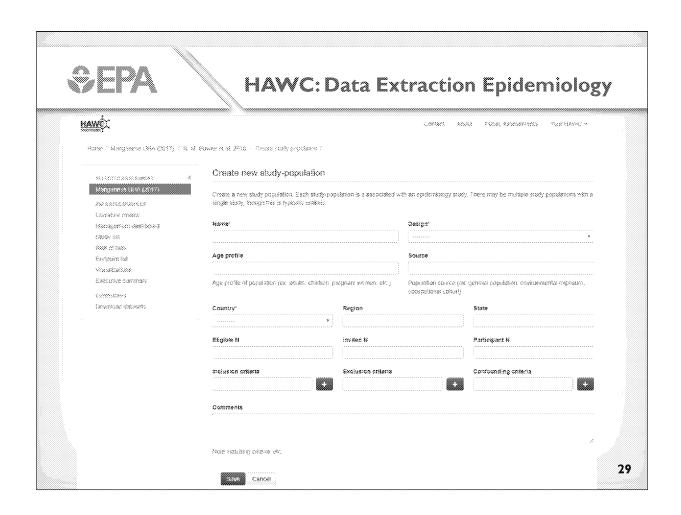




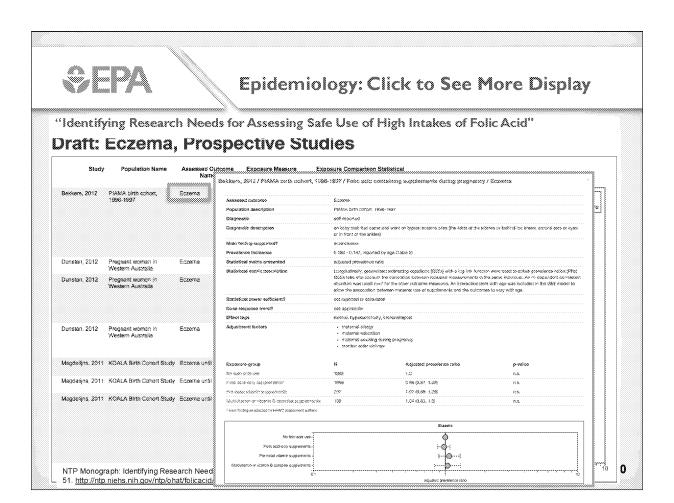




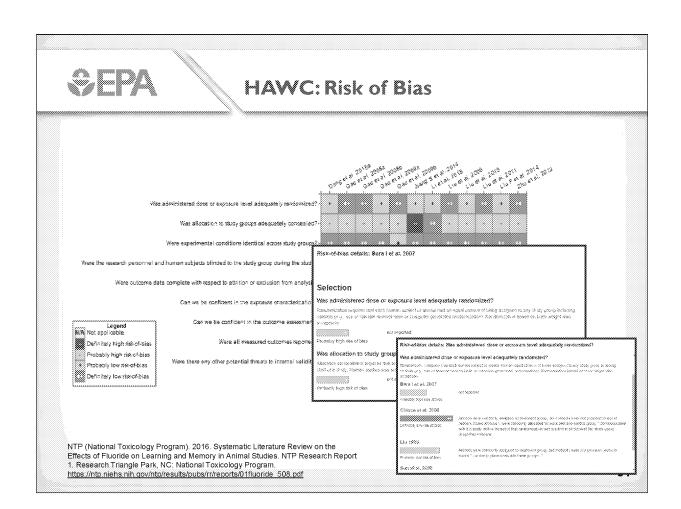




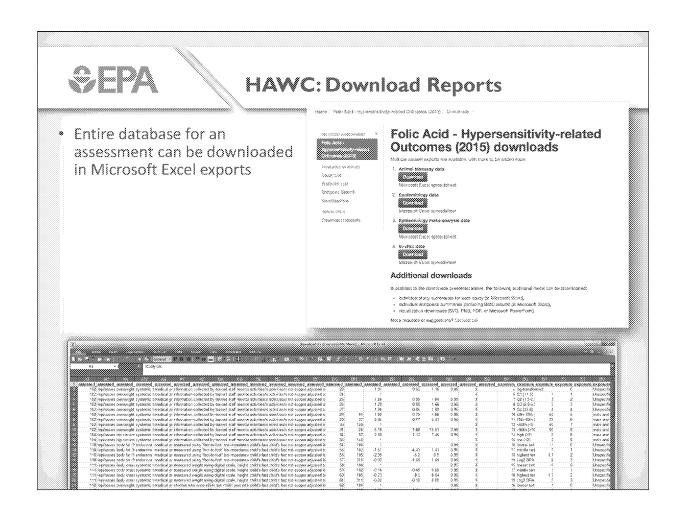
















UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR SCIENCE ADVISORY BOARD

September 1, 2017

EPA-SAB-17-008

The Honorable E. Scott Pruitt Administrator U.S. Environmental Protection Agency 1200 Pennsylvania Avenue, NW Washington, D.C. 20460

Subject: Science Advisory Board comments on EPA's response to recommendations on the Integrated Risk Information System

Dear Administrator Pruitt:

The EPA Chartered Science Advisory Board (SAB) met on August 29-30, 2017 and, as part of the meeting's agenda, received an update on the restructuring of the Integrated Risk Information System (IRIS). The Board was particularly impressed and pleased with the rapid progress that the Agency has made in responding to recommendations from the National Research Council of the National Academies of Sciences (NAS) and the SAB, with particularly notable improvements in the program over the past year. The SAB members in attendance voted unanimously that I communicate to you their enthusiasm for the IRIS program's progress.

As you may know, the NAS criticized several aspects of the IRIS program in their 2011 review of the formaldehyde assessment, recommending significant changes designed to make IRIS assessments more systematic and transparent. The NAS recommended that the program establish clearer guidelines for study selection, standardize the presentation of studies, use clear weight-of-evidence guidelines, better describe and justify assumptions to determine points of departure, explain modeling processes used to develop risk estimates, and better document the conclusions and estimation of toxicity values. In its 2014 report, the NAS commended EPA for significant progress toward implementing the recommendations of the 2011 report, although there remained additional room for improvement.

² National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764.



¹ National Research Council. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press. https://doi.org/10.17226/13142.

The SAB has observed significant enhancements in the IRIS program over the past few years, with impactful changes over the past year, and marked progress over the past six months. The changes are so extensive and positive that they constitute a virtual reinvention of IRIS. For example, it is now standard practice for the program to engage stakeholders in an early scoping and problem formulation phase, thereby allowing stakeholders to provide important input at the very beginning of the process. The program has fully adopted the principles of systematic review, and incorporated automation and publicly available software platforms to modernize the process. Finally, the IRIS documents are now more modular and structured to enhance transparency and readability.

The SAB notes that no other federal entity performs the IRIS functions, and that IRIS helps ensure consistency in chemical assessments within the Agency and across the federal government. IRIS serves the needs of regions, states and tribes, who often lack the ability to perform their own chemical risk assessments. IRIS is also well-positioned to incorporate new evidence streams such as cell-based screening and computational methods into risk assessment, which will be a major advancement over the coming years. The Board commends the Agency for making such significant improvements over a short period of time. We are optimistic that the restructured IRIS program will strengthen the scientific foundations of risk assessment and protect the health and safety of the American public.

Sincerely,

/s/

Dr. Peter S. Thorne, Chair Science Advisory Board

Enclosure

(1) Roster of SAB Members



NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board (SAB), a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The SAB is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names of commercial products constitute a recommendation for use. Reports of the SAB are posted on the EPA Web site at http://www.epa.gov/sab.



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- **Dr. Jeanne M. VanBriesen**, Duquesne Light Company Professor of Civil and Environmental Engineering, and Director, Center for Water Quality in Urban Environmental Systems (Water-QUEST), Department of Civil and Environmental Engineering, Carnegie Mellon University, Pittsburgh, PA



Dr. Elke Weber, Gerhard R. Andlinger Professor in Energy and the Environment, Professor of Psychology and Public Affairs, Woodrow Wilson School of Public and International Affairs, Princeton University, Princeton, NJ

Dr. Charles Werth, Professor and Bettie Margaret Smith Chair in Environmental Health Engineering, Department of Civil, Architectural and Environmental Engineering, Cockrell School of Engineering, University of Texas at Austin, Austin, TX

Dr. Peter J. Wilcoxen, Laura J. and L. Douglas Meredith Professor for Teaching Excellence, Director, Center for Environmental Policy and Administration, The Maxwell School, Syracuse University, Syracuse, NY

Dr. Robyn S. Wilson, Associate Professor, School of Environment and Natural Resources, Ohio State University, Columbus, OH

SCIENCE ADVISORY BOARD STAFF

Mr. Thomas Carpenter, Designated Federal Officer, U.S. Environmental Protection Agency, Washington, DC



Message

Sent: 11/30/2017 9:32:14 PM

Attachments: RE: Regarding systematic review; Research published relevant to draft IRIS assessment of Hexavalent Chromium;

Analysis that we just published "How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?"; Submission of Letter on Behalf of the ACC Formaldehyde Panel; RE: Invitation to

Attend Invited Experts Workshop on Formaldehyde; RE: Invitation to Attend Invited Experts Workshop on Formaldehyde; RE: Invitation to Attend Invited Experts Workshop on Formaldehyde; Invitation to Attend Invited

Experts Workshop on Formaldehyde



Message

From: White, Kimberly [Kimberly_White@americanchemistry.com]

Sent: 8/11/2017 11:08:33 AM

To: Thayer, Kris [thayer.kris@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]

Subject: RE: Invitation to Attend Invited Experts Workshop on Formaldehyde

Sure. I'll plan to give you a call at 1pm instead then.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602

www.americanchemistry.com

From: Thayer, Kris [mailto:thayer.kris@epa.gov]

Sent: Friday, August 11, 2017 7:08 AM **To:** White, Kimberly; Bahadori, Tina

Subject: RE: Invitation to Attend Invited Experts Workshop on Formaldehyde

Thanks! Can we make it closer to 12:30 or 1? I have a meeting ending at 12:00 that I suspect may run a little long.

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Friday, August 11, 2017 6:33 AM

To: Thayer, Kris < thayer.kris@epa.gov>; Bahadori, Tina Bahadori, Tina Bahadori, Tina Tina Tina Bahadori, Tina Tina <a href="mailto:t

Dear Kris:

Great. I will plan to give you a call at ~12:15pm (ET). I look forward to speaking with you.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly_White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602

www.americanchemistry.com

From: Thayer, Kris [mailto:thayer.kris@epa.gov]
Sent: Thursday, August 10, 2017 8:03 PM
To: White, Kimberly; Bahadori, Tina

Subject: RE: Invitation to Attend Invited Experts Workshop on Formaldehyde

Kimberly,

I will be available to attend — I'm free between 12 and 2 pm tomorrow if you want to discuss (Ex. 6 - Personal Privacy | Does that time window work for you?

Sincerely,

Kris



Kristina Thayer, Ph.D.

Director, Integrated Risk Information System (IRIS) Division National Center for Environmental Assessment, NCEA

ORD, USEPA

Mail Code: B243-01

Building: Bldg B (Room B211I) Research Triangle Park, NC 27711

(919) 541-0152 RTP

(703) 347-0260 Potomac Yards

Skype: kristina.thayer thayer.kris@epa.gov

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Wednesday, August 2, 2017 11:02 AM

To: Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>

Subject: Invitation to Attend Invited Experts Workshop on Formaldehyde

Dear Dr. Bahadori and Dr. Thayer,

I am assisting in the coordination of a 1 ½ day invited experts workshop of ~25 scientist in October 2017. The focus of the workshop will be to explore the formaldehyde science and discuss approaches for evaluating and integrating the available evidence to draw conclusions regarding human health cancer risk. Dr. Jim Swenberg and Dr. Ken Mundt have agreed to chair the workshop and we've extended invitations to a broad range of scientists from academia, industry and government. Given your activities on formaldehyde, you and your staff would be welcomed additions to the workshop and I'd like to discuss your interest and availability in participating. The workshop is tentatively planned to take place in Chapel Hill, NC and is targeted for October 10 - 11, 2017. I am working with the workshop chairs to confirm attendance to the workshop and would welcome the opportunity to discuss the tentative agenda topics and attendee list.

Feel free to give me a call (202-249-6707) or email (<u>kimberly_white@americanchemistry.com</u>) at your convenience to discuss further or let me know a good time to give you a call. Thank you for considering this invitation and I look forward to speaking with you.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com





Message

To: Hines, Ronald [Hines.Ronald@epa.gov]; Rogers, John M. [Rogers.John@epa.gov]

CC: Jones, Samantha [Jones.Samantha@epa.gov]

Subject: NHEERL and Formaldehyde

Attachments: 1 - Attendee List.pdf; 2 - Agenda.pdf

Dear Ron and John,

You may be aware that ACC is funding a meeting, co-chaired by Swenberg and Mundt. This meeting is essentially being staged in anticipation of the release of the formaldehyde IRIS assessment to the NAS for peer review.

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile: Ex.6-Personal Privacy mail: Bahadori.Tina@epa.gov



Message

From: Champlin, Anna [Champlin.Anna@epa.gov]

Sent: 2/9/2018 1:54:09 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]

Subject: RE: Need persective

FYI – JOZ and Richard suggested this response instead, which was sent to OPA.

Ex. 5 - Deliberative Process

Anna (Osaka) Champlin
National Center for Environmental Assessment
EPA Office of Research and Development
(Desk) 202-564-8074
(Cell) Ex. 6 - Personal Privacy

From: Bahadori, Tina

Sent: Thursday, February 08, 2018 1:17 PM

To: Bussard, David <Bussard.David@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Champlin, Anna <Champlin.Anna@epa.gov>

Subject: Need persective

Hi everyone

Ex. 5 - Deliberative Process

From: Champlin, Anna

Sent: Thursday, February 8, 2018 12:47 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Avery, James

<Avery.James@epa.gov>

Cc: Lehman, Rachel < lehman.rachel@epa.gov>

Subject: RE: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

Tina -

ORD comms ran our response by JOZ, \$\dag{\dag{}}

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Anna (Osaka) Champlin
National Center for Environmental Assessment
EPA Office of Research and Development
(Desk) 202-564-8074
(Cell) Ex. 6 - Personal Privacy



From: Bahadori, Tina

Sent: Wednesday, February 07, 2018 6:16 PM

To: Champlin, Anna < Champlin.Anna@epa.gov; Thayer, Kris < thayer, Kris thayer.kris@epa.gov; Avery, James

<Avery.James@epa.gov>

Cc: Lehman, Rachel < lehman.rachel@epa.gov >

Subject: RE: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

I think this is very good Anna. I made some minor edits below highlighted in yellow.

Tina

From: Champlin, Anna

Sent: Wednesday, February 7, 2018 4:02 PM

To: Bahadori, Tina < Bahadori.Tina@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>; Avery, James

<Avery.James@epa.gov>

Cc: Lehman, Rachel < lehman.rachel@epa.gov>

Subject: FW: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

Hi Tina,

Below is a draft response to a media inquiry that we received this week about the formaldehyde assessment. The reporter's questions are below and concern this article

(<u>https://www.sciencedirect.com/science/article/pii/S027323001730363X</u>) published last week. The reporter would like a response **by this Friday**.

REPORTER QUESTIONS:

- Do we have any comment we would like to make about the review?
- Do we accept the conclusions of the review?
- Are we planning to re-issue the IRIS?

DRAFT REPONSE:

Ex. 5 - Deliberative Process

Thanks,

Anna (Osaka) Champlin National Center for Environmental Assessment EPA Office of Research and Development (Desk) 202-564-8074

(Cell) Ex. 6 - Personal Privacy



From: Sauerhage, Maggie

Sent: Tuesday, February 6, 2018 9:14:54 AM

To: Lehman, Rachel; Champlin, Anna

Cc: Hubbard, Carolyn; Maguire, Megan; D'Amico, Louis

Subject: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

Hi ladies – please see below for an inquiry from Chemical Risk Manager. They're wondering if we'd like to comment on a recently published review in Regulatory Toxicology and Pharmacology which disputes a link between formaldehyde and leukemia as suggested by the 2010 draft IRIS assessment. The deadline is the end of this week.

The questions are:

- Do we any comment we would like to make about the review?
- Do we accept the conclusions of the review?
- Are we planning to re-issue the IRIS? (not entirely clear on this one)

OUTLET CHEMICAL RISK MANAGER
REPORTER JUDITH CHAMBERLAIN
DDL FRIDAY 2/9

Good morning colleagues, Can we help this reporter?

++

I work for a chemical news agency called Chemical Risk Manager, which is part of Chemical Watch and we were interested to read a review in Regulatory Toxicology and Pharmacology which disputes a link between formaldehyde and leukaemia as suggested by the 2010 draft IRIS assessment.

I wonder if you have any comment you would like to make about the review and if you accept the conclusions and also whether you are planning to re-issue the IRIS?

The review was published in a peer-reviewed journal (Regulatory Toxicology and Pharmacology) last week I think and this is the link:

https://www.sciencedirect.com/science/article/pii/S027323001730363X

If you could get a comment on this for me that would be great. Ideally I would need a response by the end of the week if possible.

Many thanks Judith





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY National Center for Environmental Assessment Washington, DC 20460

OFFICE OF RESEARCH AND DEVELOPMENT

October 06, 2017

Kimberly Wise White, Ph.D.
Senior Director
American Chemistry Council
Chemical Products and Technology Division
On Behalf of the ACC Formaldehyde Panel
700 Second St., NE
Washington, DC 20002

Dear Dr. Wise White,

Thank you for your letter of September 13, 2017 reiterating the American Chemistry Council (ACC) Formaldehyde Panel's interest in the EPA's formaldehyde IRIS assessment. I forwarded a copy of your letter and the accompanying National Toxicology Program (NTP) report to the assessment team. The assessment team is aware of this report and will be including consideration of its findings in the public comment draft of the formaldehyde assessment.

I would like to reassure you and the Panel again that we are very aware of the importance of this assessment and are mindful of your concerns. This is why we hope to complete the draft of this assessment as expeditiously as possible and make it available for public comment and peer review by the National Academy of Sciences (NAS). We are also aware that the Panel has been committed to conducting research to address the recommendations of the NAS and engaging scientists on approaches to integrate the scientific evidence for formaldehyde. As you indicated, EPA scientists will participate in the ACC-sponsored October workshop.

In your letter, you also raised a number of questions about the draft assessment which we addressed separately below. But truthfully, the only way to demonstrate our commitment to a scientifically robust and transparent formaldehyde assessment is to present the document for public comment and rigorous peer review by the NAS.



Again, thank you for your letter. Should you have further questions, you may contact me by phone (703-347-8600), or email (bahadori.tina@epa.gov).

Sincerely,

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment National Program Director, Human Health Risk Assessment U.S. EPA, Office of Research and Development

CC: Robert Kavlock Richard Yamada Kris Thayer Dan Morgan



Responses to ACC Questions on the IRIS Toxicological Review of Formaldehyde (October 2017)

1. How is EPA considering new scientific information, like the NTP study, for incorporation into the weight of evidence for the formaldehyde IRIS assessment?

EPA is carefully reviewing and considering new, peer-reviewed science as it becomes available, for inclusion in the revised draft formaldehyde assessment. We are fully incorporating the NTP study into the current draft assessment.

2. When did EPA last conduct a search of the formaldehyde literature for science to incorporate into the IRIS assessment and how frequently does EPA monitor the formaldehyde literature to identify potential studies that should be incorporated into the assessment?

The last formal literature search was completed in October, 2016, and the next formal literature search is currently underway. In addition, the assessment managers and team of scientists working on the assessment continually monitor the scientific literature for awareness and consideration of the latest available research. Our partners and stakeholders who have great interest in this assessment have remained vigilant in ensuring that all pertinent studies are brought to our attention and confirming that our formal and informal searches are complete. The NTP study is just one example of that very situation, where a document released after the last formal literature search has already been incorporated into the draft assessment, as appropriate.

3. What guidance documents or procedures will EPA utilize to evaluate study quality for studies relied upon to reach conclusions in the formaldehyde IRIS assessment? Please provide specific references if available.

EPA will be using Agency risk assessment guidelines as a framework for evaluating study quality and to reach conclusions in the draft formaldehyde assessment. Public guidance documents can easily be accessed at https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance. In addition, as you know, EPA has been incorporating principles of systematic review into the assessment development process, in response to the recommendations from the 2011 and 2014 NAS reports. The draft assessment which we hope to share with the public soon will transparently explain the procedures utilized in development of the assessment.

4. When will EPA release a weight of evidence framework illustrating how various data streams (i.e. mechanistic, toxicology and epidemiology studies) are evaluated for quality and then integrated to reach conclusions about formaldehyde?

EPA is using existing Agency guidance to weigh, synthesize, and integrate evidence to evaluate formaldehyde toxicity. The criteria used for identifying studies, evaluating quality, and integrating evidence streams, will be clearly and transparently described in the formaldehyde assessment, as was recommended by the NAS.



5. How has EPA addressed all the 2011 NAS recommendations for formaldehyde?

EPA has addressed all the 2011 NAS recommendations for formaldehyde in the revised draft assessment. A section in the appendix will clearly describe how the Agency addressed the recommendations.

6. How will EPA seek public input and peer review on the formaldehyde IRIS assessment and what types of public meetings or workshops will be held to receive input?

The revised draft formaldehyde assessment EPA will follow the established IRIS process. Following agency and interagency review, the draft assessment will be released for public comment, and an accompanying public science meeting. Following the public comment draft, EPA will make any necessary revisions, and a peer review draft will be released for independent peer review by the NAS. The NAS peer review will also include an opportunity for public comment.





November 21, 2017

Dr. Jennifer Orme-Zavaleta **Environmental Protection Agency** Deputy Assistant Administrator for Science (principal) **EPA Science Advisor** Office of Research and Development Mail code: 8101R 1200 Pennsylvania Avenue, N.W. Washington, DC 20460

Re: Recent and Ongoing Formaldehyde Science Relevant to Non-Linear Dose Response Modeling

Dear Dr. Orme-Zavaleta:

EPA's Integrated Risk Information System (IRIS) program has been working to revise the 2010 draft formaldehyde IRIS assessment in response to numerous substantive recommendations made by the National Academy of Sciences (NAS) in 2011. Concurrently, the American Chemistry Council's Formaldehyde Panel (the Panel) has supported scientific studies and evaluations of formaldehyde that are directly responsive to key recommendations made by the NAS.

In light of your recent appointment as the Deputy Assistant Administrator for Science in the Office of Research and Development, we write to call your attention to seminal research led by Dr. James Swenberg at the University of North Carolina. Dr. Swenberg's work specifically addresses the NAS recommendation to improve the understanding of when exogenous formaldehyde exposure can alter normal endogenous formaldehyde concentrations. His research findings reconcile the divergent statements made in the published literature, and noted by the NAS, as to whether rat nasal tumors form via a threshold mode of action (MOA) and whether inhaled formaldehyde can be systemically delivered.

Dr. Swenberg's research employs an innovative ultra-sensitive analytical method that can differentiate and measure endogenous versus exogenous formaldehyde DNA adducts or protein crosslinks in tissues throughout the body. This method has been applied in studies conducted in multiple laboratory species, and has been critical in illustrating that the metabolism of inhaled formaldehyde is rapid at the portal of entry so it does not move beyond the portal of entry or reach distal sites in the body including the bone marrow and circulating blood cells.

Dr. Swenberg's recent formaldehyde related publications include:

¹ National Academy of Sciences (NAS). National Research Council (NRC). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. Board of Environmental Studies and Toxicology. Division of Earth and Life Sciences.



Dr. Jennifer Orme-Zavaleta November 21, 2017 Page 2

- Edrissi et al. 2017² demonstrated formation of exogenous adducts in the nasal epithelium and, to some extent, in trachea of rats, but not in distant tissues of lung, bone marrow, or white blood cells following inhalation of concentrations of 2 ppm formaldehyde for up to 28 days.
- Lai et al. 2016 ³ found exogenous formaldehyde induced DNA protein crosslinks only in the nasal tissue of rats and monkeys, but not in tissues distant to the site of initial contact.
- Yu et al. 2015⁴ measured exogenous and endogenous DNA adducts in rats and monkeys and found that exogenous adducts accumulated in the rat nasal epithelium to reach steady state concentrations, with no exogenous adducts measured at tissues distant to the site of initial contact following exposure to concentrations of 15 ppm for up to 4 days. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively.
- Edrissi et al. 2013⁵ found that exogenous N6-formyllysine was detected in the nasal epithelium, but was not detected in the lung, liver, or bone marrow following inhalation of concentrations up to 9.1 ppm for 6 hours.
- Lu et al. 2012⁶ demonstrated that N(2)-hydroxymethyl-dG is the primary DNA adduct formed in cells following formaldehyde exposure to cells in culture. In addition, the study showed that alkylating agents induce methyl adducts at N(2)-dG and N(6)-dA positions, which are identical to the reduced forms of hydroxymethyl adducts arising from exogenous formaldehyde.
- Moeller et al. 2011⁷ found that both exogenous and endogenous adducts were readily detected and quantified in the nasal tissues of groups of monkeys exposed by inhalation to 1.9 or 6.1 ppm formaldehyde for two consecutive days, with an exposure dependent increase in exogenous adducts observed. In contrast, only endogenous adducts were detectable in the bone marrow, even though ~10 times more DNA was analyzed for this tissue than for nasal tissues. These data clearly show the formation of exogenous formaldehyde adducts in nasal DNA of primates and the lack of formation of exogenous DNA adducts in the bone marrow.

⁷ Moeller, B., Lu, K., Doyle-Eisele, M., McDonald, J., Gigliotti, A., and Swenberg, J. (2011). Determination of N 2-hydroxymethyl-dG adducts in the nasal epithelium and bone marrow of nonhuman primates following 13CD2-formaldehyde inhalation exposure. Chemical Research in Toxicology. 24(2): 162-164.





² Edrissi, B., Taghizadeh, K., Moeller, B.C., Yu, R., Kracko, D., Doyle-Eisele, M., Swenberg, J.A., and Dedon, P.C. (2017). N6-Formyllysine as a Biomarker of Formaldehyde Exposure: Formation and Loss of N6-Formyllysine in Nasal Epithelium in Long-Term, Low-Dose Inhalation Studies in Rats. Chemical Research in Toxicology30(8):1572-1576.

³ Lai, Y., Yu, R., Hartwell, H., Moeller, B., Bodnar, W., and Swenberg, J. (2016). Measurement of endogenous versus exogenous formaldehyde-induced DNA-protein crosslinks in animal tissues by stable isotope labeling and ultrasensitive mass spectrometry. Cancer Research, 76(9): 2652-2661.

⁴ Yu, R., Lai, Y., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., Bodnar, W., Starr, T., and Swenberg, J. A. (2015). Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. Toxicological Sciences, 146(1), 170-182.

Edrissi, B., Taghizadeh, K., Moeller, B., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Dedon, P. (2013). Dosimetry of N 6-Formyllysine Adducts Following [13C2H2]-Formaldehyde Exposures in Rats. Chemical Research in Toxicology. 26(10): 1421-1423.
 Lu, K., Craft, S., Nakamura, J., Moeller, B., and Swenberg, J. (2012). Use of LC-MS/MS and stable isotopes to differentiate hydroxymethyl and methyl DNA adducts from formaldehyde and nitrosodimethylamine. Chemical Research in Toxicology. 25(3): 664-675.

Dr. Jennifer Orme-Zavaleta November 21, 2017 Page 3

These results consistently demonstrate that formaldehyde is not systemically delivered. In addition to this research, other agencies have also sought to evaluate the potential impacts of exogenous exposures. A 2014 European Food Safety Authority (EFSA) scientific report⁸ evaluated endogenous formaldehyde turnover and background levels from food sources. EFSA (2014) cited literature demonstrating steady state formaldehyde concentrations in blood of 2.6 mg/L and daily endogenous turnover of 878-1310 mg formaldehyde/kg bw/day. The EFSA evaluation found that the relative contribution of exogenous formaldehyde compared to that which is systemically produced as part of normal metabolism was negligible and illustrates the utility of conducting reality check calculations to determine if exogenous formaldehyde exposures present an appreciable risk.

To further add to the weight of the scientific evidence, the Panel is currently supporting, Dr. Swenberg's research to identify threshold levels above which exogenous formaldehyde exposure alters normal endogenous formaldehyde concentrations. Specifically, this research includes a 28 day *in vivo* (nose only) inhalation study where rats were exposed to radio-labeled formaldehyde at 0, 1, 30 or 300 ppb. Following exposures, tissue samples were collected from the nasal and upper respiratory tract, lung, bone marrow, liver, cerebrum, hippocampus, olfactory bulb, blood and plasma, for analysis. The in-life portion of the study is complete and sample analysis is underway, with results expected by the end of January 2018.

Previous scientific research has supported a threshold for formaldehyde effects and has called into question EPA's use of a linear dose-response model for the estimation of an Inhalation Unit Risk (IUR) for formaldehyde. In the 2010 draft formaldehyde IRIS assessment, EPA utilized a linear dose-response model to develop an IUR. According to the EPA's 2005 Guidelines for Carcinogen Risk Assessment, the linear approach is used when there is an absence of sufficient information on MOAs for carcinogenicity or the MOA information indicates that the dose-response curve at low doses is expected to be linear. However, where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. In the case of formaldehyde, significant mechanistic data informs the formaldehyde MOA and provides evidence of an exposure threshold in the dose-response curve for carcinogenicity. The available toxicity literature provides considerable additional evidence in animals of observed thresholds for effects from formaldehyde exposure (Woutersen et al. 1989¹⁰; Casanova-Schmitz et al. 1984¹¹; Heck et al. 1990¹²; Swenberg et al. 2013¹³; and Starr and Swenberg 2016¹⁴). The work currently being

¹³ Swenberg, J.A., Moeller, B.C., Lu, K., Rager, J.E., Fry, R. and Starr, T.B. (2013). Formaldehyde Carcinogenicity Research: 30 Years and Counting for Mode of Action, Epidemiology, and Cancer Risk Assessment. Toxicologic Pathology, 41(2): 181-189.





⁸ European Food Safety Authority (EFSA) 2014. Scientific Report. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. EFSA Journal. 12(2):3550.

⁹ EPA Guidelines for Carcinogen Risk Assessment (March 2005).

Woutersen, R.A., Garderen-Hoetmer, V., Bruijntjes, J.P., Zwart, A. and Feron, V.J. (1989). Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. Journal of Applied Toxicology, 9(1): 39-46.

¹¹ Casanova-Schmitz, M., Starr, T.B., and Heck, H.D. (1984). Differentiation between Metabolic Incorporation and Covalent Binding in the Labeling of Macromolecules in the Rat Nasal Mucosa and Bone Marrow by Inhaled [14C] - and [3H] Formaldehyde. Toxicology and Applied Pharmacology, 76(1): 26-44.

¹² Heck, H.D., Casanova, M., and Starr, T.B. (1990). Formaldehyde Toxicity—New Understanding. Critical Reviews in Toxicology, 20(6): 397-426

Dr. Jennifer Orme-Zavaleta November 21, 2017 Page 4

conducted by Dr. Swenberg will further add to the weight of evidence regarding effect thresholds for formaldehyde exposure. We consider the magnitude and quality of Dr. Swenberg's work to be truly "game changing" and critical to the fuller understanding of the effects of chronic formaldehyde exposure.

The Panel has endeavored to keep staff in the IRIS program informed of relevant new scientific data as it becomes available and we will continue to do so moving forward. Panel representatives would like to meet with you in January 2018 to discuss this important science on formaldehyde and how the results support use of a non-linear approach for formaldehyde dose- response modeling. I will contact your office next week to arrange a mutually convenient time.

Sincerely,

Kimberly Wise White, PhD American Chemistry Council (ACC) Senior Director Chemical Products & Technology Division On Behalf of the ACC Formaldehyde Panel

¹⁴ Starr, T.B. and Swenberg, J.A. (2016). The bottom-up approach to bounding potential low-dose cancer risks from formaldehyde: an update. Regulatory Toxicology and Pharmacology, 77: 167-174.





439 CANNON HOUSE OFFICE BUILDING WASHINGTON, DC 20515 (202) 225-3901 FAN: (202) 225-7313

garretgraves.housa.gov

Congress of the United States

House of Representatives Washington. DC 20515—1806

September 28, 2017

The Honorable E. Scott Pruitt Administrator Office of the Administrator U.S. Environmental Protection Agency Mail code: 1101A 1200 Pennsylvania Avenue, N.W. Washington, DC 20460

Dear Administrator Pruitt.

Lam writing to express concern about the status of the Environmental Protection Agency (EPA)'s draft Integrated Risk Information System (IRIS) assessment of formaldehyde. The National Academy of Sciences harshly criticized the methodology that the EPA used to identify, evaluate and integrate the large and multi-disciplinary body of scientific studies related to the potential carcinogenicity of formaldehyde. Since 2011, the Agency has been working to revise the 2010 draft formaldehyde IRIS assessment in response to numerous substantive recommendations made by the National Academy of Sciences (NAS).

The Agency should produce regulation that protects human health from the dangers of toxic chemicals, and it should ensure that those regulatory requirements are grounded in a thorough and objective review of all the relevant scientific evidence and economic impact. I recently had the opportunity to tour one of the largest formaldehyde manufacturing plants in the country, which is located in my state. It was a reminder of the influence the facility has on the surrounding community, in addition to the many building and construction and automotive applications of this chemical.

It is my understanding that the University of North Carolina (UNC) is hosting an important scientific workshop in October, focused on a discussion of several compelling new scientific studies and new analyses of existing studies, which may have called into question the validity of the Agency's findings. A scientifically flawed, but influential, IRIS assessment will have a devastating economic impact. Furthermore, without a clear understand of the health risks associated with formaldehyde we could potentially expose the surrounding communities to even greater health risks.

For these reasons, I am respectfully requesting that you commit to withholding any further action on the development of the draft IRIS assessment of formaldehyde until the findings from the upcoming science workshop at UNC are fully considered and those findings are appropriately incorporated. It is my hope the deliberations of this important workshop will help inform the Agency on how to appropriately integrate the best available human and animal data to draw conclusions about potential cancer risks.

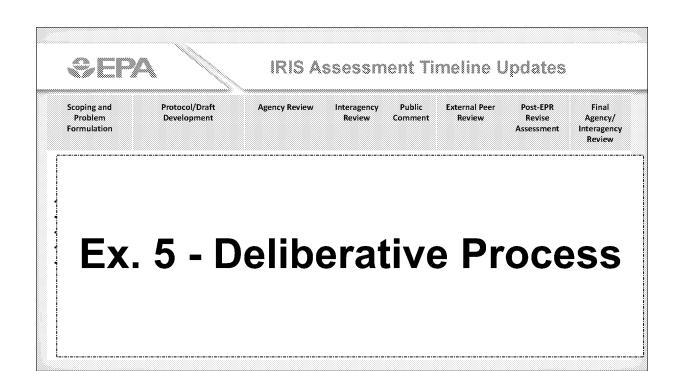


Before the risk values embedded in the Agency's assessment are used in regulatory decision making, I encourage the Agency to ensure that the regulations governing the manufacturing of formaldehyde are grounded in sound science. To me, the health and safety of the community is a paramount concern. Acting without the best or accurate science will leave a devastating impression on the American people that the Agency cannot take lightly.

Garret Graves

Member of Congress







From: Soto, Vicki [Soto.Vicki@epa.gov]

Sent: 11/16/2017 1:40:59 PM

To: Jones, Samantha [Jones.Samantha@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Avery, James

[Avery.James@epa.gov]; Shams, Dahnish [Shams.Dahnish@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; D'Amico,

Louis [DAmico.Louis@epa.gov]

CC: Lavoie, Emma [Lavoie.Emma@epa.gov]
Subject: RE: Chemicals on the IRIS agendas

Attachments: IRIS Assessments - status and various agendas.xlsx

Flag: Follow up

Ok – I've updated based on Samantha's comments. I will set up a meeting. - Vicki



Ex. 5 - Deliberative Process

From: Jones, Samantha

Sent: Wednesday, November 15, 2017 11:40 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Soto, Vicki <Soto.Vicki@epa.gov>; Avery, James <Avery.James@epa.gov>;

Shams, Dahnish <Shams.Dahnish@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>

Cc: Lavoie, Emma < Lavoie. Emma@epa.gov> **Subject:** RE: Chemicals on the IRIS agendas

Ex. 5 - Deliberative Process

Samantha

Samantha Jones, PhD
NCEA Associate Director for Health (acting)
HHRA Interim Deputy National Program Director



From: Bahadori, Tina

Sent: Wednesday, November 15, 2017 11:29 PM

To: Soto, Vicki <Soto. Vicki@epa.gov>; Jones, Samantha <Jones. Samantha@epa.gov>; Avery, James

<<u>Avery James@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; D'Amico,

Louis < DAmico. Louis@epa.gov>

Cc: Lavoie, Emma < Lavoie. Emma@epa.gov > Subject: RE: Chemicals on the IRIS agendas

This is great – and yes, please, let's schedule a follow up meeting.

Tina

From: Soto, Vicki

Sent: Wednesday, November 15, 2017 10:39 PM

To: Jones, Samantha < Jones. Samantha@epa.gov >; Bahadori, Tina < Bahadori. Tina@epa.gov >; Avery, James

<<u>Avery.James@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; D'Amico,

Louis < DAmico.Louis@epa.gov>

Cc: Lavoie, Emma < Lavoie. Emma@epa.gov > Subject: Chemicals on the IRIS agendas

Hi – here is an annotated list of chemicals from the tables on the MYA. I've attached the spreadsheet that can be sorted different ways.

I think I had scheduled a follow up meeting for us to keep discussing and then I had to cancel because of conflicts. Should I schedule something to get back together? Dahnish said there was some additional discussions about publishing our current efforts and an FR to ask for input. Let me know.

PS – Dahnish said we didn't need the 2012 agenda material, but I had already added it so it is still in this list.





Ex. 5 - Deliberative Process

From: Jones, Samantha

Sent: Thursday, November 02, 2017 1:57 PM

To: Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Avery, James <<u>Avery.James@epa.gov</u>>;

Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>

Subject: RE: IRIS agenda - assessment status.docx

I saw that Vicki has scheduled time for another discussion when we can all be there. Understanding we are going to do some discussion via email. I wanted to suggest that we take this table and cross-walk with the two tables in the MYA to ensure that we have all of the chemicals documented, identifying the status, and including text that describes the next step. Can you guys create this table and circulate to the group prior to next week's meeting?

From: Bahadori, Tina

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To: Soto, Vicki <Soto, Vicki@epa.gov>; Avery, James <Avery.James@epa.gov>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>;

D'Amico, Louis < DAmico.Louis@epa.gov>

Subject: RE: IRIS agenda - assessment status.docx

OK, this is great. How up to date is it?

From: Soto, Vicki

Sent: Wednesday, November 1, 2017 9:55 AM

To: Avery, James <<u>Avery.James@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Thayer, Kris

<thayer.kris@epa.gov>; Bahadori, Tina <Bahadori, Tina@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>;

D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>> **Subject:** IRIS agenda - assessment status.docx

This is the document that I was talking about where we currently are with chemicals on the agenda....



From: Thayer, Kris [thayer.kris@epa.gov]

Sent: 11/16/2017 7:19:07 AM

To: Soto, Vicki [Soto.Vicki@epa.gov]; Avery, James [Avery.James@epa.gov]; Persad, Amanda

[Persad.Amanda@epa.gov]; Boone, Amanda [Boone.Amanda@epa.gov]; Ross, Christine [Ross.Christine@epa.gov];

Shams, Dahnish [Shams.Dahnish@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]

CC: Rieth, Susan [Rieth.Susan@epa.gov]; Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Lee, Janice

[Lee.JaniceS@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Garcia, Kelly [garcia.kelly@epa.gov]; Lavoie, Emma

[Lavoie.Emma@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]

Subject: RE: IRIS meetings and agendas

I'm fine leading the full IMC – I don't know yet of specific topics yet..

From: Soto, Vicki

Sent: Wednesday, November 15, 2017 10:27 PM

To: Thayer, Kris <thayer.kris@epa.gov>; Avery, James <Avery, James@epa.gov>; Persad, Amanda

<Persad.Amanda@epa.gov>; Boone, Amanda <Boone.Amanda@epa.gov>; Ross, Christine <Ross.Christine@epa.gov>;

Shams, Dahnish <Shams.Dahnish@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Cc: Rieth, Susan <Rieth.Susan@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Lee, Janice

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<Lavoie.Emma@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>;

Soto, Vicki <Soto.Vicki@epa.gov>

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Title	State Date:	Agenda
iAs ERC Follow-up Discussion	11/20/2017	
IRIS Mgmt Meeting	11/20/2017	
All Scientists	11/22/2017	 RoB share HAWC tips for data extraction and RoB (Kris – 15 min) Protocol 2-3 mins Project Management Update Mn assessment plan update Retreat update
		Move to 11/30.
IMC Full	11/23/2017	
IRIS Mgmt Meeting	11/27/2017	
Agency webinar briefing - SR Protocol	11/28/2017	Share Protocol Template - 2/3 week of agency review.
NAS planning meeting	11/28/2017	
SAB biweekly meeting	11/29/2017	





From: Lavoie, Emma [Lavoie.Emma@epa.gov]

Sent: 11/16/2017 4:32:26 AM

To: Soto, Vicki [Soto.Vicki@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Avery, James [Avery.James@epa.gov]; Persad,

Amanda [Persad.Amanda@epa.gov]; Boone, Amanda [Boone.Amanda@epa.gov]; Ross, Christine

[Ross.Christine@epa.gov]; Shams, Dahnish [Shams.Dahnish@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]

CC: Rieth, Susan [Rieth.Susan@epa.gov]; Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Lee, Janice

[Lee.JaniceS@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Garcia, Kelly [garcia.kelly@epa.gov]; D'Amico,

Louis [DAmico.Louis@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]

Subject: RE: IRIS meetings and agendas

This is a helpful quick reference, thanks Vicki.

-Emma

Tel: 202 564 7091

From: Soto, Vicki

Sent: Wednesday, November 15, 2017 10:27 PM

To: Thayer, Kris <thayer.kris@epa.gov>; Avery, James <Avery.James@epa.gov>; Persad, Amanda

<Persad.Amanda@epa.gov>; Boone, Amanda <Boone.Amanda@epa.gov>; Ross, Christine <Ross.Christine@epa.gov>;

Shams, Dahnish <Shams.Dahnish@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

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<Lavoie.Emma@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>;

Soto, Vicki <Soto.Vicki@epa.gov>

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NAS planning meeting	11/28/2017
SAB biweekly meeting	11/29/2017
IMC Branch Chief	11/30/2017 Make Full IMC





From: Soto, Vicki [Soto.Vicki@epa.gov]

Sent: 11/16/2017 3:39:29 AM

To: Jones, Samantha [Jones.Samantha@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Avery, James

[Avery.James@epa.gov]; Shams, Dahnish [Shams.Dahnish@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; D'Amico,

Louis [DAmico.Louis@epa.gov]

CC: Lavoie, Emma [Lavoie.Emma@epa.gov]

Subject: Chemicals on the IRIS agendas

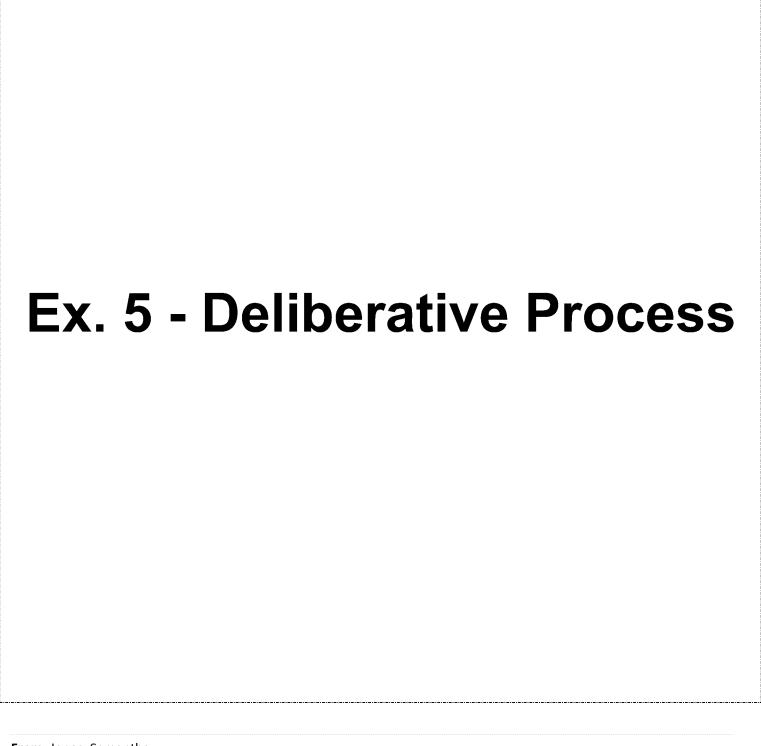
Attachments: IRIS Assessments - status and various agendas.xlsx

Hi – here is an annotated list of chemicals from the tables on the MYA. I've attached the spreadsheet that can be sorted different ways.

I think I had scheduled a follow up meeting for us to keep discussing and then I had to cancel because of conflicts. Should I schedule something to get back together? Dahnish said there was some additional discussions about publishing our current efforts and an FR to ask for input. Let me know.

PS – Dahnish said we didn't need the 2012 agenda material, but I had already added it so it is still in this list.





From: Jones, Samantha

Sent: Thursday, November 02, 2017 1:57 PM

 $\textbf{To:} \ \ \textbf{Bahadori, Tina} < \textbf{Bahadori.Tina@epa.gov}; \ \textbf{Soto, Vicki} < \textbf{Soto.Vicki@epa.gov}; \ \textbf{Avery, James} < \textbf{Avery.James@epa.gov}; \ \textbf{Soto, Vicki@epa.gov}; \ \textbf{Avery, James} < \textbf{Avery.James} < \textbf{$

Shams, Dahnish <Shams.Dahnish@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; D'Amico, Louis

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Sent: Wednesday, November 1, 2017 9:55 AM

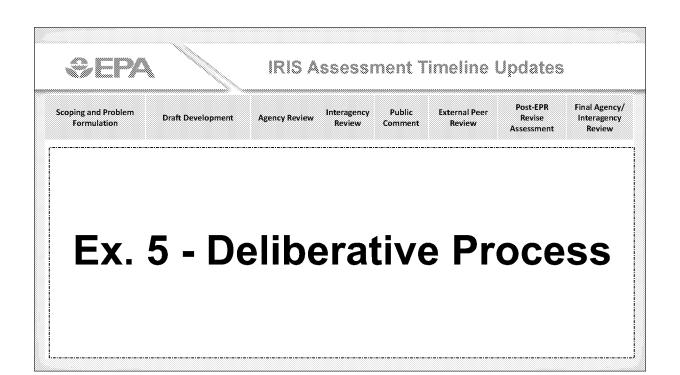
To: Avery, James <<u>Avery, James@epa.gov</u>>; Shams, Dahnish <<u>Shams, Dahnish@epa.gov</u>>; Thayer, Kris

<<u>thayer.kris@epa.gov</u>>; Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Jones, Samantha <<u>Jones, Samantha@epa.gov</u>>;

D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>> **Subject:** IRIS agenda - assessment status.docx

This is the document that I was talking about where we currently are with chemicals on the agenda....









Upcoming IRIS Assessment Products



Step 0a	Draft Development	Agency/Interagency Review	Public Comment/External Peer Review	Revise Assessment	Final Agency/Interagency Review	



Previous agenda:

Acetaldehyde (MYA) Acrylonitrile Ammonia (MYA) Arsenic Benzo(a)pyrene Beryllium Biphenyl n-butanol Tert-butanol BBP Acute? Started Completed In progress halted	
Ammonia (MYA) Arsenic Benzo(a)pyrene Beryllium Biphenyl n-butanol Tert-butanol BBP Started In progress In progress Lambda In progress In progress	
Arsenic In progress Benzo(a)pyrene Completed Beryllium Biphenyl n-butanol halted Tert-butanol In progress BBP halted	
Benzo(a)pyrene Completed Beryllium Biphenyl n-butanol halted Tert-butanol In progress BBP halted	
Beryllium Biphenyl n-butanol halted Tert-butanol In progress BBP halted	
Biphenyl n-butanol halted Tert-butanol In progress BBP halted	
n-butanol halted Tert-butanol In progress BBP halted	
BBP halted	
BBP halted	
Cadmium (MYA)	
Chloroethane	
Chloroform In progress	
Chromium VI In progress	
Cobalt	
Copper	
6 phthalates	
1,2-dichlorobenzene (MYA)	
1,3-dichlorobenzene (MYA)	
1,4-dichlorobenzene (MYA)	
DEP Halted	
di(2-ethylhexyl) adipate	
di(2-ethylhexyl) phthalate (MYA)	
DIBP Halted	
DINP Halted	
1,4-Dioxane Completed?	
dipentyl phthalate	
ETBE In progress	
Ethylbenzene In progress	
EtO Completed	
Formaldehyde In progress	
HBCD In progress	
Hexachlorobutadiene	
RDX In progress	
Libby amphibole Completed	
Methanol (cancer)	
Methanol (noncancer)	
MTBE (MYA)	



IRIS Assessments – Status with MYA

Naphthalene	In progress
Nickel (MYA)	
Halogenated platinum salts and platinum	
compounds	
PCBs (noncancer)	In progress
PAH mixtures	In progress
Styrene (MYA)	
2,3,7,8-tetrachlorodibenzo-p-dioxin	
TMBs	Completed
Uranium	In progress
Vanadium pentoxide	Halted
Vinyl acetate	



From: Bussard, David [Bussard.David@epa.gov]

Sent: 9/26/2017 2:01:49 PM

To: Avery, James [Avery.James@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Bussard, David

[Bussard.David@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Dutton, Steven [Dutton.Steven@epa.gov]; Gatchett, Annette [Gatchett.Annette@epa.gov]; Hagerthey, Scot [Hagerthey.Scot@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Lehman, Rachel [lehman.rachel@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]; Tewolde, Salina [tewolde.salina@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Troyer, Michael [Troyer.Michael@epa.gov]; Vandenberg, John [Vandenberg.John@epa.gov]; Birchfield, Norman

[Birchfield.Norman@epa.gov]; Bierwagen, Britta [Bierwagen.Britta@epa.gov]; Morozov, Viktor

[Morozov.Viktor@epa.gov]; Saint, Chris [Saint.Chris@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]

Subject: Wash Div Weekly

Attachments: 2017-09-26 Washington Division.docx

Attached is Wash Div Weekly. [Tina clearly knows about the formaldehyde briefing for the IOAA, but I added it for the sake of the other NCEA Divisions.]

David A. Bussard

Director, Washington Division
National Center for Environmental Assessment (NCEA)
Office of Research and Development, USEPA

Washington Division National Center for Environmental Assessment Weekly Report: Sept 26, 2017

Presentations, Public Meetings, Workshops and Events

- Working Group on Critical Loads of Atmospheric Deposition. Christopher Clark (NCEA EARCG) is leading a discussion series of the Working Group on Critical Loads of Atmospheric Deposition, on how to combine critical loads of nitrogen and sulfur deposition for tree species for decision making across the EPA, US Forest Service, and the National Parks Service (8/3, 8/17, 9/7, 9/21).
- Interagency Sustained Assessment Working Group (SAWG). On September 20, Chris Weaver (NCEA EARCG) will participate in a panel discussion organized by SAWG on contributor (e.g., author, reviewer, etc.) participation and engagement in national and international climate assessments.
- North American Diatom Symposium. Sylvia Lee (NCEA EARCG) will be presenting at the North American Diatom Symposium at Stone Lab, Gibraltar Island, Ohio on September 27 October 1. Her presentation is entitled, "Harmonizing and revising diatom taxonomy in existing bioassessment datasets for use as indicators," which describes work with U.S. Geological Survey (USGS) and Office of Water colleagues. She is co-presenting a talked entitled, "Status of the Diatoms of the United States web flora," a bioassessment tool supported in part by Office of Water. In addition, Dr. Lee is a co-author on 3 student posters (including research on diatom sex and diatoms in bug guts) resulting from her teaching activities at lowa Lakeside Laboratory.
- Sustainable and Healthy Communities (SHC) monthly call. On Thursday, September 28, Robert Sabo (NCEA EARCG ORISE) will be presenting at the SHC monthly call on the National Inventory for Reactive Nitrogen (Nr Inventory). This is a project under SHC 4.61.4 that compiles downscaled information on major fluxes and pools



for Reactive Nitrogen across the contiguous U.S. to support decision making on nitrogen management from local to regional scales.

- **EPA Office of Water--Oceans Coasts Branch Meeting presentation.** On October 2, Jordan West (NCEA EARCG) will give a presentation at OW on adaptation planning frameworks (CIVA 2.9), including the climate-smart framework and Adaptation Design Tool demonstrated for coral reefs through the Corals & Climate Adaptation Planning (CCAP) project.
- Air & Waste Management Association (A&WMA) 2017 Conference. On October 10-11, Marissa Liang (NCEA EARCG ORISE) will be presenting at the A&WMA 2017 Conference "Finding Common Ground on Climate Change Mitigation and Adaption" at Arlington, Virginia. Her presentation is entitled "Assessment of Coastal Community Waste Management Vulnerabilities to Sea Level Rise and Storm Surge Use of Decision Support Tools", which describes work under project CIVA-3.1 working with Susan Julius (NCEA EARCG), NRMRL colleagues, and EPA contractors. This presentation is co-authored by Susan Julius, NRMRL colleagues (Ozge Kaplan and Susan Thorneloe), and Keith Weitz from RTI.
- Hampton Roads Adaptation Forum. On October 13, Chris Weaver (NCEA EARCG) will be giving a presentation entitled, "New Federal Sea Level Rise Scenarios for the U.S. Coastline," at the Hampton Roads Sea Level Rise/Flooding Adaptation Forum. The presentation will describe the new set of global and regional sea level rise scenarios developed by the USGCRP and the Subcommittee on Ocean Science and Technology (SOST) Interagency Sea Level Rise Task Force to the coastal scientists and engineers participating in the forum.

Internal Briefings

• Formaldehyde IRIS assessment. On September 26, NCEA briefed Bob Kavlock and Bruce Rodan on how the IRIS assessment of formaldehyde toxicity will address potential quantification of the myeloid leukemia cancer risks of inhaled formaldehyde. We expect the assessment document should be ready for Agency review within a month.

Recognition / Accolades

• Associate Editorship, *Drug & Chemical Toxicology*. Dr. Suryanarayana Vulimiri (NCEA) has been selected to be an Associate Editor of the journal *Drug & Chemical Toxicology*



Washington Division National Center for Environmental Assessment Weekly Report: Sept 26, 2017

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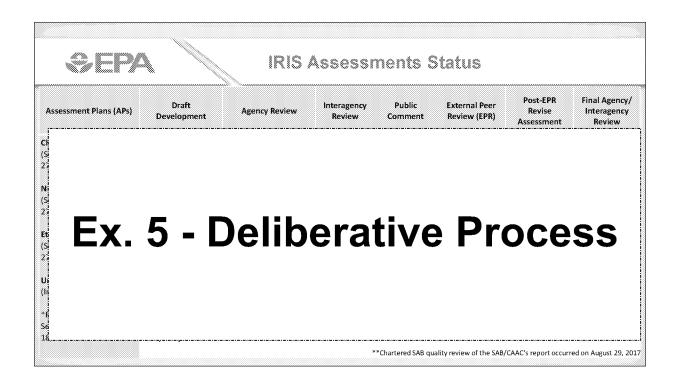
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From: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

Sent: 11/7/2017 1:55:14 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Robbins, Chris [Robbins.Chris@epa.gov]; Rodan, Bruce

[rodan.bruce@epa.gov]; Yamada, Richard (Yujiro) [yamada.richard@epa.gov]

CC: Christian, Megan [Christian.Megan@epa.gov]; McPherson, Mark [McPherson.Mark@epa.gov]; Sjogren, Mya

[Sjogren.Mya@epa.gov]; Fleming, Megan [Fleming.Megan@epa.gov]; Plotkin, Viktoriya [Plotkin.Viktoriya@epa.gov];

Kuhn, Kevin [Kuhn.Kevin@epa.gov]; Blackburn, Elizabeth [Blackburn.Elizabeth@epa.gov]; Perry, Dale

[Perry.Dale@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Lang, Jamie [Lang.Jamie@epa.gov]; Heckman,

Deborah [Heckman.Deborah@epa.gov]; Burman, Eric [Burman.Eric@epa.gov]

Subject: RE: For your review -- IRIS Report to Congress

Thanks Tina, I believe Richard also had a few edits. If those are addressed then we're good to go

Jennifer Orme-Zavaleta, PhD USEPA Office of Research and Development

DC RTI Ex. 6 - Personal Privacy 915

orme-zavaleta.jennifer@epa.gov

From: Bahadori, Tina

Sent: Tuesday, November 07, 2017 8:05 AM

To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Robbins, Chris <Robbins.Chris@epa.gov>; Rodan,

Bruce <rodan.bruce@epa.gov>; Yamada, Richard (Yujiro) <yamada.richard@epa.gov>

Cc: Christian, Megan < Christian.Megan@epa.gov>; McPherson, Mark < McPherson.Mark@epa.gov>; Sjogren, Mya < Sjogren.Mya@epa.gov>; Fleming, Megan < Fleming.Megan@epa.gov>; Plotkin, Viktoriya < Plotkin.Viktoriya@epa.gov>; Viktoriya@epa.gov>; Plotkin, Viktoriya@epa.gov>; Plotkin

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Deborah < Heckman. Deborah@epa.gov>; Burman, Eric < Burman. Eric@epa.gov>

Subject: For your review -- IRIS Report to Congress

Good Morning Jennifer, Chris, Bruce, and Richard,

Attached for your review is the current draft of the IRIS Report to Congress in response to the FY17 appropriations language. This version reflects the edits provided by Bob, Bruce, and Maureen. This (short) relates report primarily to the formation of the Interagency workgroup that was cochaired by ORD and OMB/OIRA, and the peer review of the formaldehyde assessment.

Once IOAA review is completed and concerns addressed, OPARM will transmit this to OCFO.

Please let me know if you have any questions and would like more information.

Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile: Ex.6-Personal Privacy Email: Bahadori.Tina@epa.gov





From: Blackburn, Elizabeth [Blackburn.Elizabeth@epa.gov]

Sent: 11/7/2017 1:19:14 PM

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CC: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Robbins, Chris [Robbins.Chris@epa.gov]; Rodan, Bruce

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[Christian.Megan@epa.gov]; McPherson, Mark [McPherson.Mark@epa.gov]; Sjogren, Mya [Sjogren.Mya@epa.gov];

Fleming, Megan [Fleming.Megan@epa.gov]; Plotkin, Viktoriya [Plotkin.Viktoriya@epa.gov]; Kuhn, Kevin

[Kuhn.Kevin@epa.gov]; Perry, Dale [Perry.Dale@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Lang, Jamie [Lang.Jamie@epa.gov]; Heckman, Deborah [Heckman.Deborah@epa.gov]; Burman, Eric [Burman.Eric@epa.gov]

Subject: Re: For your review -- IRIS Report to Congress

Oops - sorry all. The review has been completed so no need for further review. Maureen will send to OPARM when she gets in.

Thank you!

Sent from my iPhone

On Nov 7, 2017, at 8:04 AM, Bahadori, Tina < Bahadori, Tina@epa.gov> wrote:

Good Morning Jennifer, Chris, Bruce, and Richard,

Attached for your review is the current draft of the IRIS Report to Congress in response to the FY17 appropriations language. This version reflects the edits provided by Bob, Bruce, and Maureen. This (short) relates report primarily to the formation of the Interagency workgroup that was cochaired by ORD and OMB/OIRA, and the peer review of the formaldehyde assessment.

Once IOAA review is completed and concerns addressed, OPARM will transmit this to OCFO.

Please let me know if you have any questions and would like more information.

Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile Ex. 6 - Personal Privacy mail: <u>Bahadori, Tina@epa.gov</u>

<IRIS IWG Report to Congress _11-03-17.docx>



From: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

Sent: 1/16/2018 8:37:08 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]
Subject: Re: Meeting with ACC on Formaldehyde

Good

Sent from my iPad

On Jan 16, 2018, at 3:18 PM, Bahadori, Tina <Bahadori. Tina@epa.gov> wrote:

OAR and OP are going to join this briefing.

Τ.

----Original Appointment----

From: Gentry, Nathan On Behalf Of Orme-Zavaleta, Jennifer

Sent: Tuesday, January 16, 2018 11:23 AM

To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan;

Kuhn, Kevin; Bahadori, Tina

Cc: Vandenberg, John; Thayer, Kris; Lavoie, Emma; Axelrad, Daniel; Ross, Mary; Bussard, David

Subject: Meeting with ACC on Formaldehyde

When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41213 RRB/via video to B249

From: White, Kimberly [mailto:Kimberly_White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta.Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21st letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22nd to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006.

[Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulator y implications of new science in evaluating formaldehyde leukemogenicity.

<u>Mundt KA¹</u>, <u>Gentry PR²</u>, <u>Dell LD²</u>, <u>Rodricks JV²</u>, <u>Boffetta P³</u>. **Author information**

Abstract



Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRISreview and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

KEYWORDS:

Epidemiology;	Evidence i	integration;	Hazard ev	aluation; <i>I</i>	Mechanisti	c studies;	Regulator	y science;
Toxicology								

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2nd Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com



From: D'Amico, Louis [DAmico.Louis@epa.gov]

Sent: 2/15/2018 5:48:35 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]
CC: Champlin, Anna [Champlin.Anna@epa.gov]

Subject: Draft ACC Formaldehyde Response.

Attachments: ACC Formaldehyde Panel Letter to EPA - January 26 2018 - Final.pdf; ACC FA Response_Feb18_draft1.docx

Hi Tina,

Here you go. Let me know if it's too pithy for a "generic" response. I could throw in a couple more generic sentences about the advances IRIS has made in systematic review and assessment development, but I thought people might be aiming for short and sweet.

Anna, I'm pulling you into this editing process as we go, so you can see the back and forth (and since you're working on the FA factsheet right now).

(NOTE NEW CONTACT

INFORMATION)

Louis D'Amico, Ph.D.

Assistant Center Director, Communications and Regulatory Support (Acting)

National Center for Environmental Assessment

Associate Director for Policy and Communications

Human Health Risk Assessment National Research Program

U.S. EPA - Office of Research and Development

Mail Code 8601R | 1200 Pennsylvania Ave, NW | Washington, DC 20460

Office: 202-564-4605 | Mobile Ex. 6 - Personal Privacy email: damico.louis@epa.gov





January 26, 2018

Dr. Jennifer Orme-Zavaleta
Environmental Protection Agency
Deputy Assistant Administrator for Science (Principal)
EPA Science Advisor
Office of Research and Development
Mail code: 8101R
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Dear Dr. Orme-Zavaleta:

Thank you for meeting with members of the American Chemistry Council's Formaldehyde Panel (the Panel) on January 24, 2018. The meeting provided the Panel with an opportunity to stress the importance of producing a revised formaldehyde IRIS assessment that fully implements and resolves scientifically the recommendations of the 2011 National Academy of Sciences (NAS) report. The Panel left the meeting very alarmed and troubled that the revised draft formaldehyde IRIS assessment will not utilize a mode of action framework as the organizing principle to assess hazard and dose response. Further, during the meeting Dr. Bahadori indicated that the revised draft IRIS assessment has not revisited the science but instead will be a restructuring of the draft. Notably the previous draft relied on studies that have been shown in recent years to have significant scientific and methodological issues^{2,3}. The Panel is unsure what is meant by "restructuring" but what was previously missing from the draft formaldehyde IRIS assessment was the consideration of mode of action in drawing conclusions. Given the significant amount of science generated for this chemical and the resources committed by the American taxpayers, a revised draft IRIS assessment must revisit all previous conclusions, demonstrate effective and science-based integration of all the lines of evidence and meet the standards of scientific integrity and transparency requested by the NAS and the public.

Additionally, during our meeting the Panel inquired about the regulatory drivers for an updated final formaldehyde IRIS assessment. EPA's Office of Air and Radiation (OAR) staff indicated that they had some activities for completion in 2018 that could be informed if a final revised IRIS assessment was available. EPA staff indicated that the revised draft formaldehyde IRIS assessment is unlikely to be finalized in 2018 due to the necessary and critical internal and external review required. Thus, a final IRIS assessment would not be available to inform the upcoming OAR activities. Given this information, the Panel was surprised to learn that OAR staff will consider the 1989 final IRIS assessment as best available science even though the

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¹ National Academy of Sciences (NAS). National Research Council (NRC). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. Board of Environmental Studies and Toxicology. Division of Earth and Life Sciences.

² Mundt, K., Gallagher, A., Dell, L., Natelson, E., Boffetta, P., and Gentry, R. Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells? (2017) Critical Reviews in Toxicology. Aug;47(7):592-602.

³ Gentry, R., Rodricks, J., Turnbull, D., Bachand, A., Van Landingham, C., Shipp, A., Albertini, R., and Irons, R. (2013). Formaldehyde exposure and leukemia: Critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility.

Critical Reviews in Toxicology 43, no. 8: 661-670.

science of formaldehyde has vastly evolved over the last 29 years. The Clean Air Act requires reliance on the best available science and we strongly encourage OAR to use a more recently updated regulatory standard or develop its own formaldehyde risk value, for use in pending activities instead of relying on an outdated 1989 value. Notably, EPA has independently developed values for use in risk assessment related air activities in the past⁴.

The Panel has proactively supported cutting-edge research with leading scientists that directly addresses and informs the 2011 NAS recommendations, resulting in several dozen peer reviewed publications. The state of the science has evolved to the point where it is clear that using mode of action as the organizing framework is scientifically justified and necessary in drawing conclusions. The current assumption that any level of formaldehyde exposure results in some level of potential cancer risk, is inconsistent with the available recognized mode of action for this chemical. A "restructuring" of the 2010 draft assessment will not meet the EPA's scientific responsibility to make sound public policy decisions. As discussed during our meeting these new scientific studies demonstrate:

- 1. The biological implausibility of any relationship between formaldehyde inhalation and leukemia.
- 2. A threshold mode of action for any potential adverse health effects at the portal of entry.
- 3. The importance and utility of mode of action science for understanding potential impacts from inhalation exposure to formaldehyde.
- 4. The need for transparent integration of all streams of scientific evidence (epidemiology, toxicology and mode of action information) to draw scientifically defensible conclusions regarding human health risk

The integration of mode of action evidence is a key element in an overall weight of the evidence assessment. Failure to account for this scientific evidence in revising a draft formaldehyde IRIS assessment would erroneously suggest that none of these available data inform understanding of cancer risks in the low concentration region, which is most important to understanding potential daily human exposures.

As stated in our meeting, a premature release of a draft assessment that has not followed the full IRIS review process or benefited from the sound scientific advice received during that process will cause irreparable harm to the companies represented by the Panel and to the many companies and jobs that depend on the broad use of the chemical; ACC estimates that approximately 963,000 jobs depend on the use of formaldehyde. The Panel urges you to ensure that the revised draft formaldehyde IRIS assessment can be held to the highest scientific standards. This involves fully implementing and resolving all the NAS recommendations; transparently identifying, evaluating, and integrating the available data using mode of action as the organizing framework; and recognizing that a threshold approach for portal of entry effects is supported by overwhelming evidence. I again reiterate, that the Panel is extremely concerned that a revised draft

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⁴ April 29, 2004 EPA Office of Air Quality Planning & Standards tabulated dose-response values used in the risk assessment of hazardous air pollutants. In 2004, the Air Office indicated that it did not plan to use the 1987 dose-response value reported in IRIS as it no longer represented the best available science in the peer-reviewed literature. See April 2008 GAO Report titled "EPA's New Assessment Process Will Increase Challenges EPA Faces in Evaluating and Regulating Chemicals" for full details. Webpage: https://www.gao.gov/new.items/d08743t.pdf

January 26, 2018 Page 3

formaldehyde IRIS assessment that does not meet these benchmarks will also not meet NAS's original intentions in making its 2011 recommendations and fail to build public confidence in the scientific rigor and value of assessments produced by the IRIS program.

Sincerely,

Kimberly Wise White, Ph.D. American Chemistry Council (ACC) Senior Director, Chemical Products and Technology Division On Behalf of the ACC Formaldehyde Panel

The Honorable Scott Pruitt, Administrator Mr. Ryan Jackson, Chief of Staff The Honorable William Wehrum, Assistant Administrator, Office of Air and Radiation



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From: Lavoie, Emma [Lavoie.Emma@epa.gov]

Sent: 9/26/2017 4:04:18 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Bussard, David

[Bussard.David@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

CC: Soto, Vicki [Soto.Vicki@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov];

Shams, Dahnish [Shams.Dahnish@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]; D'Amico, Louis

[DAmico.Louis@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]

Subject: RE: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

Sorry for any email confusion.

-Emma

Emma T. Lavoie, PhD Tel: 703-347-0328

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:02 PM

To: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Bussard, David < Bussard. David@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>

Cc: Soto, Vicki <Soto.Vicki@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara

<Glenn.Barbara@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>;

D'Amico, Louis <DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

٠.

From: Ramasamy, Santhini

Sent: Tuesday, September 26, 2017 12:00 PM

To: Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Lavoie, Emma

<Lavoie.Emma@epa.gov>

Cc: Soto, Vicki <Soto, Vicki@epa.gov>; Bahadori, Tina <Bahadori, Tina@epa.gov>; Kraft, Andrew

<Kraft_Andrew@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>;

Jones, Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>; Ross, Mary

<Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

From: Bussard, David

Sent: Tuesday, September 26, 2017 11:42 AM

To: Thayer, Kris < thayer.kris@epa.gov>; Lavoie, Emma < Lavoie.Emma@epa.gov>

Cc: Soto, Vicki < Soto. Vicki@epa.gov >; Bahadori, Tina < Bahadori. Tina@epa.gov >; Kraft, Andrew

< Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha



<<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>> **Subject:** RE: Next Steps on Formaldehyde

Yes to all this.

Ex. 5 - Deliberative Process

David

From: Thayer, Kris

Sent: Tuesday, September 26, 2017 11:39 AM **To:** Lavoie, Emma < <u>Lavoie</u>, Emma@epa.gov>

Cc: Soto, Vicki <Soto. Vicki@epa.gov>; Bahadori, Tina <Bahadori, Tina@epa.gov>; Kraft, Andrew

< Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: Re: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

Sent from my iPhone

On Sep 26, 2017, at 9:05 AM, Lavoie, Emma < Lavoie. Emma@epa.gov> wrote:

That's all good to hear.

Ex. 5 - Deliberative Process

-Emma

Emma T. Lavoie, PhD Tel: 703-347-0328

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 8:27 AM

To: Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Bussard, David < Bussard. David@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Lavoie, Emma < Lavoie. Emma@epa.gov >

Cc: Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico, Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

Subject: FW: Next Steps on Formaldehyde

Hi Everyone,



Ex. 5 - Deliberative Process

Just so we are all on the same page, Andrew and Barbara, can you tell me again when the documents will be ready for transmittal – the overview, the main body of assessment, and appendices. I think we said end of October for the first two? What about the appendices? Once we put this information out there, I would like us to be able to adhere to it. So, can you please confirm?

Other thoughts?

Τ.

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) < yamada.richard@epa.gov>

Cc: Kavlock, Robert <Kavlock.Robert@epa.gov>; Rodan, Bruce <rodan.bruce@epa.gov>; Orme-

Zavaleta, Jennifer < Orme-Zavaleta.Jennifer@epa.gov>; Gwinn, Maureen

<gwinn.maureen@epa.gov>; Sjogren, Mya <Sjogren.Mya@epa.gov>; Kuhn, Kevin

<<u>Kuhn.Kevin@epa.gov</u>>; Fegley, Robert <<u>Fegley.Robert@epa.gov</u>>; Ross, Mary

< Ross. Mary@epa.gov>; Jones, Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Bussard, David

<Bussard.David@epa.gov>

Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday — I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices — Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile Ex. 6 - Personal Privacy hail: Bahadori. Tina@epa.gov



Message

From: Thayer, Kris [thayer.kris@epa.gov]

Sent: 12/14/2017 10:09:15 AM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]
CC: Glenn, Barbara [Glenn.Barbara@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]

Subject: RE: Formaldehyde IRIS assessment

Thanks Andrew for letting us know...

From: Kraft, Andrew

Sent: Wednesday, December 13, 2017 3:44 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>

Subject: FW: Formaldehyde IRIS assessment

FYI, Tina and Kris, in light of the recent briefing for Jennifer, just FYI that we have had some communication with the Health Canada folks recently. We provided the typical response...

From: Deveau, Michelle (HC/SC) [mailto:michelle.deveau@canada.ca]

Sent: Thursday, September 28, 2017 4:10 PM **To:** Kraft, Andrew < <u>Kraft.Andrew@epa.gov</u>> **Subject:** Formaldehyde IRIS assessment

Hi Andrew,

We met briefly at your poster session at SOT 2016 (in New Orleans). I'm with the indoor air group at Health Canada, and we're thinking of reassessing our Residential Indoor Air Quality Guideline for formaldehyde. I was wondering if you'd be able to provide any information to me on your expected timelines for your IRIS assessment on formaldehyde. Are you still moving forward with updating your assessment? And do you have any approximate timelines on when you hope to have a draft published?

Your assessment is something that we would potentially be considering quite a bit if we did decide to reassess our guideline, so it would be very helpful if you are able to provide any possible information for us.

Thanks in advance for any information you can give me, Michelle

Michelle Deveau, MSc(A), ROH

Senior Scientific Evaluator, Indoor Air Contaminants Assessment Section, Healthy Environments and Consumer Safety Branch

Health Canada / Government of Canada michelle.deveau@canada.ca / Tel: 613-948-8920

PLEASE NOTE MY NEW E-MAIL ADDRESS

Évaluatrice scientifique principale, Section d'évaluation des contaminants de l'air intérieur, Direction générale de la santé environnementale et de la sécurité des consommateurs

Santé Canada / Gouvernement du Canada





Message

Thayer, Kris [thayer.kris@epa.gov] From:

Sent: 11/17/2017 8:25:48 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]

Subject: RE: conflict

okay

From: Bahadori, Tina

Sent: Friday, November 17, 2017 3:24 PM To: Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: conflict

I just talked to Jennifer

Ex. 5 - Deliberative Process

but

you and I did not have to participate. I think we need to take the naphthalene meeting, but, we could walk over and

listen to the last 30 minutes of the FA meeting, if we wanted to...or not.

Τ.

From: Thayer, Kris

Sent: Friday, November 17, 2017 3:18 PM To: Bahadori, Tina < Bahadori. Tina@epa.gov>

Subject: RE: conflict

So, do we do this or naphthalene or this?

From: Bahadori, Tina

Sent: Friday, November 17, 2017 3:14 PM To: Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: conflict

Dr. Kenneth Mundt, of Ramboll-Environ, will provide a brief on the highlights of the October 10-11, 2017 Formaldehyde Science Workshop at UNC-Chapel Hill. Dr. Mundt will also present on the current state of the science on formaldehyde carcinogenicity

From: Thayer, Kris

Sent: Friday, November 17, 2017 3:01 PM To: Bahadori, Tina < Bahadori, Tina@epa.gov>

Subject: RE: conflict

I'm on a call now. Ugh. I'm dying to know. Are you free later? Or hints?

From: Bahadori, Tina

Sent: Friday, November 17, 2017 2:59 PM To: Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: conflict

You're not going to believe it.



From: Thayer, Kris

Sent: Friday, November 17, 2017 2:31 PM **To:** Bahadori, Tina 8ahadori.Tina@epa.gov

Subject: RE: conflict

No clue

From: Bahadori, Tina

Sent: Friday, November 17, 2017 2:31 PM **To:** Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: conflict

Do you know what this is even about? Workshop report out??

From: Thayer, Kris

Sent: Friday, November 17, 2017 1:51 PM **To:** Bahadori, Tina 8ahadori.Tina@epa.gov

Subject: conflict

This conflicts with our napthalene meeting – I assume we need to re-schedule with Jennifer?

por root. Their factors are constituted	ııme *	INOTES	\		s x sousseed we go	*
Delete Resp	ond	Meeting N., Calen	dar Quick Steps	5. Move	Tags	rs. Es
	an on behalf of C shop Report Ou)rme-Zavaleta, Jen t	nifer M Bennett,)	ohn; 🏿 Mitchell, Claudi	ette; 🌉 Rodan, Br	uce; 🏾 Bahadori,
Retention Policy		inbo	ix (Never)		Expires Never	
Please respond. This appointment conflic	ts with another one	on your calendar.				
When Tuesday, December 1	I2, 2017 10:30 AM-11:	30 AM Location	RTP Main Campus Rm D3	01; Videoconference :	call Stuce and Tin	13

Kristina Thayer, Ph.D.

Director, Integrated Risk Information System (IRIS) Division National Center for Environmental Assessment, NCEA

Mail Code: B243-01

ORD, USEPA

Building: Bldg B (Room B211I) Research Triangle Park, NC 27711

(919) 541-0152 RTP

(202) 564-1771 Potomac Yards

Skype: kristina.thayer thayer.kris@epa.gov



Message

From: Kuhn, Kevin [Kuhn.Kevin@epa.gov]

Sent: 1/24/2018 7:19:16 PM

To: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Rodan, Bruce [rodan.bruce@epa.gov]; Yamada, Richard

(Yujiro) [yamada.richard@epa.gov]; Fleming, Megan [Fleming.Megan@epa.gov]; Christian, Megan

[Christian.Megan@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]

CC: Vandenberg, John [Vandenberg.John@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Lavoie, Emma

[Lavoie.Emma@epa.gov]; Axelrad, Daniel [Axelrad.Daniel@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Mazza, Carl [Mazza.Carl@epa.gov]; Sasser, Erika [Sasser.Erika@epa.gov]; Rimer, Kelly [Rimer.Kelly@epa.gov]; Vasu, Amy [Vasu.Amy@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn,

Barbara [Glenn.Barbara@epa.gov]

Subject: RE: Meeting with ACC on Formaldehyde

Attachments: background.pdf; formaldehyde ppt.pdf; one pager.pdf; paper.pdf

Hi All,

Please find attached the background documents under discussion.

Kevin Kuhn ORD/EPA

(202) 564-4835

Mobile: Ex. 6 - Personal Privacy

-----Original Appointment-----From: Orme-Zavaleta, Jennifer

Sent: Monday, December 4, 2017 12:07 PM

To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin;

Bahadori, Tina

Cc: Vandenberg, John; Thayer, Kris; Lavoie, Emma; Axelrad, Daniel; Ross, Mary; Bussard, David; Mazza, Carl; Sasser,

Erika; Rimer, Kelly; Vasu, Amy; Kraft, Andrew; Glenn, Barbara

Subject: Meeting with ACC on Formaldehyde

When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41213 RRB/via video to B249; call-in **Ex. 6 - Personal Privacy**

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21st letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22nd to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

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<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA¹, Gentry PR², Dell LD², Rodricks JV², Boffetta P³. Author information

Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

KEYWORDS:

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology

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Kind Regards,

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Background

In 2011, the NAS completed its review of the EPA's draft IRIS assessment¹ and made recommendations for improving the evaluation of carcinogenicity, toxicity and dose-response modeling in the IRIS assessment. The American Chemistry Council Formaldehyde Panel has been committed to generating new science that directly addresses the specific recommendations made by the NAS. The below summary provides an overview of some of the available scientific evidence that illustrate a lack of causal association of formaldehyde and leukemia; and a need to integrate all the available formaldehyde data to reach conclusion.

Epidemiological Evidence

The NAS report recommended reviewing determinations of causality for specific lymphohematopoietic (LHP) cancers, and reviewing the criteria that were used to weigh evidence and assess causality. In addition, because the draft IRIS assessment relies heavily on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas) is also needed, as well as clarification of the basis of EPA's interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. Additionally, the NAS also recommended resolving the conflicting statements in the IRIS assessment concerning which upper respiratory cancer sites were found to be causally associated with formaldehyde exposure. Below are several studies that focus on these areas.

- Mundt, K., Gallagher, A., Dell, L., Natelson, E., Boffetta, P., and Gentry, R. Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells? (2017) Critical Reviews in Toxicology. Aug;47(7):592-602. Conducted additional and refined analysis on the key underlying data (including specifically exposure information which had not been previously provided) utilized in a study relied upon in the draft IRIS assessment (e.g. Zhang et al. 2010). The analysis evaluates exposed and unexposed populations and any potential correlations between formaldehyde exposure and aneuploidy among the exposed populations. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Additionally, among formaldehyde-exposed workers, no association was observed between individual formaldehyde exposure estimates and frequency of aneuploidy, which the original study authors suggested were indicators of myeloid leukemia risk. *Work Supported by the ACC Formaldehyde Panel members.
- Marsh, G., Morfeld, P., Zimmerman, S., Liu, Y., and Balmert, L. (2016). An updated reanalysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study." Journal of Occupational Medicine and Toxicology 11, no. 1: 1. The reanalysis provided little or no evidence to support NCI's suggestion of a persistent association between formaldehyde exposure and mortality from nasopharyngeal cancer. Specifically, the findings led to: (1) reduced standardized mortality ratios and relative risks in the remaining nine study plants in unaffected exposure categories, (2) attenuated exposure-response relations for formaldehyde and nasopharyngeal cancer for all the formaldehyde metrics considered and (3) strengthened and expanded evidence that the earlier NCI internal analyses were non-robust and mis-specified as they did not account for a statistically significant interaction structure between

¹ NAS 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. National Research Council. ISBN: 0-309-21194-8, 194 pages. Available at: http://www.nap.edu/catalog/13142.html.



EPA-18-0076-A-000152

plant group (Plant 1 vs. Plants 2-10) and formaldehyde exposure. *Work supported by the ACC Formaldehyde Panel members.

- Checkoway, H., Dell, L.D., Boffetta, P., Gallagher, A.E., Crawford, L., Lees, P.S., and Mundt, K.A. (2015). Formaldehyde exposure and mortality risks from acute myeloid leukemia and other Lymphohematopoietic Malignancies in the US National Cancer Institute cohort study of workers in Formaldehyde Industries. Journal of Occupational and Environmental Medicine, 57(7), 785-794. Authors obtained the data from the NCI cohort study via a Technology Transfer Agreement to replicate the findings reported by Beane Freemen et al. (2009) and to conduct additional analysis of associations of specific leukemias and lymphomas, especially acute myeloid leukemia, with formaldehyde exposure. Analyses were conducted including peak exposure as defined by Beane Freeman et al. (2009), as well as using an alternative more standard definition of peak exposure. The findings from this re-analysis fail to support the hypothesis that formaldehyde causes acute myeloid leukemia. Specifically, the results indicated: Acute myeloid leukemia was unrelated to "peak" or any other formaldehyde metric including the conventional cumulative exposure (also as reported in Beane Freeman (2009)). In fact, very few cohort members had any peak exposure within 20 years of death due to AML. There were suggestive associations with peak exposure only for chronic myeloid leukemia, albeit based on very small numbers. No other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. *Work supported by the ACC Formaldehyde Panel members. Work recognized by the American College of Occupational and Environmental Medicine (ACOEM's) Journal of Occupational and Environmental Medicine (JOEM) for a 2017 Kammer Merit in Authorship Award.
- Coggon, D., Ntani, G., Harris, E. C., & Palmer, K. T. (2014). Upper airway cancer, myeloid leukemia, and other cancers in a cohort of British chemical workers exposed to formaldehyde. American Journal of Epidemiology, 179(11), 1301-1311. Conducted an update of mortality data through 2012 for the UK cohort of 14,008 formaldehyde users and producers and reported no increased mortality from myeloid leukemia (SMR 1.16, 95% CI 0.60 -2.20 for background exposure; SMR=1.46, 95% CI 0.84 2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450 -1.82 for high exposure). In a nested case-control analysis of 45 myeloid leukemias (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was increased (non-statistically significant) among workers exposed to high concentrations for < 1 year (OR=1.77, 95% CI 0.45 7.03), workers exposed to high concentrations ≥ 1 year showed no increased risk (OR 0.96, 95% CI 0.24 3.82)
- Talibov, M., Lehtinen-Jacks, S., Martinsen, JI., Kjærheim, K., Lynge, E., Sparén, P., Tryggvadottir, L., Weiderpass, E., Kauppinen, T., Kyyrönen, P., Pukkala, E. (2014). Occupational exposure to solvents and acute myeloid leukemia: a population-based, casecontrol study in four Nordic countries Scandinavian Journal of Work, Environment & Hhealth 40.5: 511. Analyzed 15,332 newly diagnosed cases of AML (i.e., not deaths) diagnosed from 1961 to 2005 in Finland, Norway, Sweden, and Iceland, and 76,660 matched controls. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (HR 0.89, 95% CI 0.81 0.97 for workers exposed to ≤0.171 ppm-years; HR 0.92, 95% CI 0.83 -1.03 for workers



exposed to 0.171 - 1.6 ppm-yrs, and HR=1.17, 95% CI 0.91 - 1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde).

- Marsh, G., Morfeld, P., Collins, J., Symons, JM. (2014). Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. Journal of Occupational Medicine and Toxicology 9, no. 1: 1. Evaluation concluded that efforts should be made to reanalyze data from the 2004 follow-up of the National Cancer Institute formaldehyde cohort study. The evaluation also recommended that publications resulting from the National Cancer Institute formaldehyde cohort study which contain incorrect data from the incomplete 1994 mortality follow-up should be retracted entirely or corrected via published errata in the corresponding journals. * Work supported by the ACC Formaldehyde Panel members.
- Meyers, AR, Pinkerton, LE, Hein, MJ. (2013). Cohort mortality study of garment industry workers exposed to formaldehyde: Update and internal comparisons. AmJ IndMed 56(9):1027-39. Updated mortality data from 1960 through 2008 for 11,043 US garment workers employed at least three months between 1955 and 1983 at three US factories and exposed to formaldehyde. A total of 36 leukemia deaths were reported (SMR=1.04, 95% CI 0.73 1.44, compared to US mortality rates), of which 21 were myeloid leukemia (14 AML, 5 CML, 2 other and unspecified ML). The SMR for AML was 1.22 (95% CI 0.67 2.05), noting that "the extended follow-up did not strengthen previously observed associations."
- Saberi Hosnijeh, F., Christopher, Y., Peeters, P., Romieu, I., Xun, W., Riboli, E., Raaschou-Nielsen, O., Tjønneland, A., Becker, N., Nieters, A., Trichopoulou, A., Bamia, C., Orfanos, P., Oddone, E., Luján-Barroso, L., Dorronsoro, M., Navarro, C., Barricarte, A., Molina-Montes, E., Wareham, N., Vineis, P., and Vermeulen, R. (2013). Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC)Occup Environ Med;70:464-470. Studied occupational risk factors among 671 incident leukemia cases (201 ML, including 113 AML, and 237 lymphoid leukemia) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy. Occupational exposures were estimated using a general population exposure matrix that classified occupational codes of study subjects into categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). No increased risk of AML was associated with low exposure to formaldehyde (HR 1.01, 95% CI 0.65 1.57) and no AML cases occurred among individuals in the high formaldehyde exposure category.

Toxicological Evidence

The NAS noted the paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. Two studies, as summarized below, have been conducted by the National Toxicology Program to further evaluate the potential for LHPs in animals.

• Morgan, DL., Dixon, D., Jokinen, MP., King, DH., Price, H., Travlos, G., Herbert, RA., French, JW., and Waalkes, MP. Evaluation of a potential mechanism for formaldehyde-induced leukemia in p53-haploinsufficient mice. (2015). Society of Toxicology Annual Meeting, Abstract #1637. The research reported on a study testing the hypothesis that formaldehyde may cause leukemia by causing genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. Despite the fact that the study used mice pre-disposed to the development of lymphohematopoietic cancers, the results provided indicated that formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in the mice. (Draft technical report currently under internal NTP review).



• Morgan, DL., Dixon, D., Jokinen, MP., King, DH., Price, H., Travlos, G., Herbert, RA., French, JE., and Waalkes, MP. Evaluation of a potential mechanism for formaldehyde-induced leukemia in C3B6.129F1-Trp53tm1Brd mice. (2014). Society of Toxicology Annual Meeting, Poster Board -129. Study found that no cases of leukemia or lymphohematopoietic neoplasia were seen in genetically predisposed C3B6.129F1-Trp53tm1Brd mice exposed to formaldehyde through inhalation.(Draft technical report currently under internal NTP review).

Mechanistic Evidence

The NAS noted that systemic responses are unlikely to arise from the direct delivery of formaldehyde to a distant site in the body and that the experimental evidence is insufficient to support the hypothesis that circulating hematopoietic stem cells may be the target cells for the mutagenic effects that eventually lead to cancers. The NAS also noted a need for improved understanding of exogenous and endogenous formaldehyde concentrations. Below are several studies that focus on these areas.

- Albertini, R. J., & Kaden, D. A. (2016). Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?. Critical Reviews in Toxicology, 1-40. Research focused on the critical review and integration of the available peer-reviewed literature addressing the potential genotoxicity of formaldehyde. This publication also addresses the potential involvement of chromosome changes in blood cells suggested to be key events in proposed modes of action for the development of leukemia following formaldehyde exposure. The evaluation found reported genetic changes in circulating blood cells do not provide convincing support for formaldehyde classification as a human leukemogen. Specifically, the evaluation notes that no convincing evidence that exogenous exposures to formaldehyde alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect specifically not in the bone marrow. In addition, recent studies reporting changes in human bone marrow or hematopoietic precursor cells either have had confounding exposures or could not distinguish in vivo from in vitro occurrences. *Work supported by the ACC Formaldehyde Panel members.
- Lai, Y., Yu, R., Hartwell, H. J., Moeller, B. C., Bodnar, W. M., & Swenberg, J. A. (2016). Measurement of Endogenous versus Exogenous Formaldehyde-Induced DNA-Protein Crosslinks in Animal Tissues by Stable Isotope Labeling and Ultrasensitive Mass Spectrometry. Cancer Research, 76(9), 2652-2661. Examined the formation, accumulation, and hydrolysis of DNA-protein crosslinks of both exogenous and endogenous formaldehyde. The results show that inhaled formaldehyde only reached rat and monkey noses, but not tissues distant to the site of initial contact. *Work supported by the ACC Formaldehyde Panel members.
- Yu, R., Lai, Y., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., Bodnar, W., Starr, T., & Swenberg, J. A. (2015). Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. Toxicological Sciences, 146(1), 170-182. Evaluated the plausibility for inhaled formaldehyde to reach distal sites in rat and monkey models. The study indicated that inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. *Work supported by the ACC Formaldehyde Panel members.
- Edrissi, B., Taghizadeh, K., Moeller, B., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Dedon, P. (2013). Dosimetry of N 6-Formyllysine Adducts Following [13C2H2]-Formaldehyde Exposures in Rats. Chemical Research in Toxicology 26, no. 10: 1421-1423. The research found that Exogenous N6-formyllysine was detected in the nasal epithelium, but was not detected in the lung, liver, or bone marrow. Endogenous adducts dominated at all exposure conditions, The results parallel previous studies of formaldehyde-induced DNA adducts. *Work supported by the ACC Formaldehyde Panel members.



- Gentry, R., Rodricks, J., Turnbull, D., Bachand, A., Van Landingham, C., Shipp, A., Albertini, R., and Irons, R. (2013). Formaldehyde exposure and leukemia: Critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility. Critical Reviews in Toxicology 43, no. 8: 661-670. A critical review of the study, as well as a reanalysis of the underlying data, was performed and the results of this reanalysis suggested factors other than formaldehyde exposure may have contributed to the effects reported. Specifically, in the original study the authors did not follow their stated protocol and evaluation of the other study data indicates that the aneuploidy measured could not have arisen in vivo, but rather arose during in vitro culture. The results of the critical review and reanalysis of the data do not support a mechanism for a causal association between formaldehyde exposure and myeloid or lymphoid malignancies. *Work supported by the ACC Formaldehyde Panel members.
- Rager, J., Moeller, B., Miller, S., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Fry, R. (2014). Formaldehyde-associated changes in microRNAs: tissue and temporal specificity in the rat nose, white blood cells, and bone marrow. Toxicological Sciences: 138(1):36-46. doi:10.1093/toxsci/kft267. In this study, a multi-tiered approach was employed to enable an understanding of the genome-wide miRNA responses to formaldehyde and to establish how these responses relate to alterations in transcriptional profiles over time and in various tissues. This study found that formaldehyde inhalation exposure induces tissue and time-dependent responses at the genomic and epigenomic level. Formaldehyde exposure disrupts miRNA expression profiles within the rat nose and white blood cells but not within the bone marrow. *Work supported by the ACC Formaldehyde Panel members.
- Rager, J., Moeller, B., Doyle-Eisele, M., Kracko, D., Swenberg, J., and Fry, R. (2013). Formaldehyde and epigenetic alterations: microRNA changes in the nasal epithelium of nonhuman primates." Environmental Health Perspectives (Online) 121, no. 3: 339. Research found that Formaldehyde exposure significantly disrupts miRNA expression profiles within the nasal epithelium. These results provide evidence for a relationship between formaldehyde exposure and altered signaling of the apoptotic machinery, likely regulated via epigenetic mechanisms. *Work supported by the ACC Formaldehyde Panel members.
- Lu, K., Craft, S., Nakamura, J., Moeller, B., and Swenberg, J. (2012). Use of LC-MS/MS and stable isotopes to differentiate hydroxymethyl and methyl DNA adducts from formaldehyde and nitrosodimethylamine." Chemical Research in Toxicology 25, no. 3: 664-675. Research demonstrated that N(2)-hydroxymethyl-dG is the primary DNA adduct formed in cells following formaldehyde exposure. In addition, the study shows that alkylating agents induce methyl adducts at N(2)-dG and N(6)-dA positions, which are identical to the reduced forms of hydroxymethyl adducts arising from formaldehyde. *Work supported by the ACC Formaldehyde Panel members.
- Moeller, B., Lu, K., Doyle-Eisele, M., McDonald, J., Gigliotti, A., and Swenberg, J. (2011). Determination of N 2-hydroxymethyl-dG adducts in the nasal epithelium and bone marrow of nonhuman primates following 13CD2-formaldehyde inhalation exposure. Chemical Research in Toxicology 24, no. 2: 162-164. Research found that both exogenous and endogenous adducts were readily detected and quantified in the nasal tissues of both exposure groups, with an exposure dependent increase in exogenous adducts observed. In contrast, only endogenous adducts were detectable in the bone marrow, even though ~10 times more DNA was analyzed. * Work supported by the ACC Formaldehyde Panel members.
- Andersen, M. E., Clewell, H. J., Bermudez, E., Dodd, D. E., Willson, G. A., Campbell, J. L., & Thomas, R. S. (2010). Formaldehyde: Integrating dosimetry, cytotoxicity and genomics to



understand dose-dependent transitions for an endogenous compound. Toxicological Sciences, kfq303. In this study, concentration and exposure duration transitions in formaldehyde mode of action were examined with pharmacokinetic modeling and with histopathology and gene expression in nasal epithelium from rats exposed to concentrations of up to 15 ppm formaldehyde for up to 13 weeks. The results of the study indicated that formaldehyde concentrations below 1 or 2 ppm would not increase risk of cancer in the nose or any other tissue or affect formaldehyde homeostasis within epithelial cells. * Work supported by the ACC Formaldehyde Panel members.

• Andersen, M. E., Clewell, H. J., Bermudez, E., Willson, G. A., & Thomas, R. S. (2008). Genomic signatures and dose-dependent transitions in nasal epithelial responses to inhaled formaldehyde in the rat. Toxicological Sciences, 105(2), 368-383. Research included repeated and acute exposure studies to assess time and concentration-dependencies of nasal responses to formaldehyde and genomic changes. The study noted that the most sensitive gene changes were associated with extracellular components and plasma membrane. There were temporal and concentration-dependent transitions in epithelial responses and genomic signatures between 0.7 and 6 ppm. * Work supported by the ACC Formaldehyde Panel members.

Dose- Response and Modeling Evidence

The NAS noted that the biologically based dose response (BBDR) model for formaldehyde is one of the best developed BBDR models to date and recommended utilizing the BBDR model in the IRIS assessment. Below are a few studies that highlight approaches for dose response analysis in line with the NAS committee recommendation.

- Van Landingham, C., Mundt, K. A., Allen, B. C., and Gentry, P. R. (2016). The need for transparency and reproducibility in documenting values for regulatory decision making and evaluating causality: The example of formaldehyde. Regulatory Toxicology and Pharmacology, 81, 512-521. This evaluation was in response to the NAS comment to conduct independent analysis of the dose-response models used in the IRIS assessment to confirm the degree to which the models fit the data appropriately The authors reported that the documentation of the methods applied in the EPA IRIS assessment lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the Beane Freeman et al. (2010). This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. *Work supported by the ACC Formaldehyde Panel members.
- Starr, T. B., & Swenberg, J. A. (2016). The bottom-up approach to bounding potential low-dose cancer risks from formaldehyde: An update. Regulatory Toxicology and Pharmacology, 77, 167-174. Updated a previously proposed method (Starr and Swenberg 2013). This approach has useful applications for substances, like formaldehyde, where there is a substantial endogenous exposure in potential target tissues and little or no empirical evidence of a positive dose-response at low exogenous exposure levels. It also provides valid bounding estimates of added risk from exposure to all airborne formaldehyde concentrations up to and including 2 ppm. *Work supported by the ACC Formaldehyde Panel members.
- Schroeter, J., Campbell, J., Kimbell, J., Conolly, R., Clewell, H., and Andersen, M. (2014) "Effects of endogenous formaldehyde in nasal tissues on inhaled formaldehyde dosimetry predictions in the rat, monkey, and human nasal passages." Toxicological Sciences 138, no. 2 (2014): 412-424. Pharmacokinetic modeling was conducted to evaluate the impact of endogenous concentrations of formaldehyde at the portal of entry. Endogenous formaldehyde in nasal tissues



did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations.

• Starr, T. B., & Swenberg, J. A. (2013). A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. Regulatory Toxicology and Pharmacology, 65(3), 311-315. Provided a refined approach for conducted risk extrapolations using a bottom up instead of top-down risk calculation. Results indicate that top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. *Work supported by the ACC Formaldehyde Panel members.

Critical Reviews and Data Integration Evidence

The NAS committee indicated that the IRIS assessment should review the discussion of asthma causation and the selected approach to establish the points of departure. The NAS also recommended that the IRIS program overall should provide more clarity in the evaluation and integration of the scientific evidence. Below are a few articles that inform the formaldehyde science in line with the NAS committee recommendations.

- Mundt, K., Gentry, PR., Dell, L., Rodricks, J., and Boffetta, P. (2017). Six years after the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity. Regul Toxicol Pharmacol. 2017 Nov 20. pii: S0273-2300(17)30363-X. Evaluates the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. Indicated that overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of lymphohematopoietic malignancies (LHM) has increased substantially. The new evidence been published in each of the major streams of evidence (i.e., human, animal and mechanistic) consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the National Research Council (2011) scientific criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure. *Work Supported by the ACC Formaldehyde Panel members.
- Golden, R., and Holm, S. (2017). Indoor Air Quality and Asthma: Has Unrecognized Exposure to Acrolein Confounded Results of Previous Studies? Dose Response. Feb 15;15(1). The evaluation illustrated that there is no evidence that indicates increased sensitivity to sensory irritation to formaldehyde in people often regarded as susceptible such as asthmatics. Suggest that previous studies on potential risk factors and childhood asthma may be confounded by formaldehyde acting as an unrecognized proxy for acrolein. *Work supported by the ACC Formaldehyde Panel members.
- Nielsen, G.D., Larsen, S.T. and P. Wolkoff. (2016) Re-evaluation of the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Arch. Toxicol. doi:10.1007/s0204-016-7133-8. Provides a summary of new key studies conducted since 2013, which were evaluated and compared to the WHO guideline. The authors concluded the overall the credibility of the WHO guideline (that recognizes threshold effects for any potential carcinogenic responses) has not been challenged by new studies.



- Rhomberg, L. (2015). Contrasting directions and directives on hazard identification for formaldehyde carcinogenicity." Regulatory Toxicology and Pharmacology: RTP 73, no. 3: 829-833. The article examined two separate National Academy of Sciences committee evaluations on whether formaldehyde should be identified as a human carcinogen. It highlighted key differences in the approaches, scientific methods and criteria used by two government agencies in identifying and classifying human carcinogens. It also discussed the importance of clear processes for evaluating science and how the available formaldehyde science illustrates the contrast between the two approaches when evidence is integrated to reach conclusions on hazard. *Work supported by the ACC Formaldehyde Panel members.
- Swenberg, J., Moeller, B., Lu, K., Rager, J., Fry, R., and Starr, T. (2013). Formaldehyde Carcinogenicity Research 30 Years and Counting for Mode of Action, Epidemiology, and Cancer Risk Assessment. Toxicologic Pathology 41(2):181-189. doi:10.1177/0192623312466459. Article reviews the data for rodent and human carcinogenicity, early mode of action studies, more recent molecular studies of both endogenous and exogenous DNA adducts, and epigenetic studies. It goes on to demonstrate the power of these research studies to provide critical data to improve our ability to develop science-based cancer risk assessments, instead of default approaches. *Work Supported by the ACC Formaldehyde Panel members.
- Checkoway, H., Boffetta, P., Mundt, D., and Mundt, K. (2012). Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies." Cancer Causes & Control 23, no. 11: 1747-1766. Evaluation found that there is no consistent or strong epidemiologic evidence that formaldehyde is causally related to any of the lymphohematopoietic malignancies. Specifically, the evaluation noted that findings from occupational cohort and population-based case-control studies were very inconsistent for lymphohematopoietic malignancies, including myeloid leukemia. Apart from some isolated exceptions, relative risks were close to the null, and there was little evidence for dose-response relations for any of the lymphohematopoietic malignancies. *Work supported by the ACC Formaldehyde Panel members.
- Rhomberg, L., Bailey, L., Goodman, J., Hamade, A., and Mayfield, D. (2011). Is exposure to formaldehyde in air causally associated with leukemia?—A hypothesis-based weight-of-evidence analysis. Critical Reviews in Toxicology 41, no. 7: 555-621. The evaluation concluded that the case for a causal association is weak and strains biological plausibility. *Work Supported by the ACC Formaldehyde Panel members.
- Golden, R. (2011). Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards. Critical Reviews in Toxicology 41, no. 8: 672-721. The assessment concluded that a formaldehyde indoor air limit of 0.1 ppm should protect even particularly susceptible individuals from both irritation effects and any potential cancer hazard. *Work supported by the ACC Formaldehyde Panel members.



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Commentary

Six years after the NRC review of EPA's *Draft IRIS Toxicological Review of Formaldehyde*: Regulatory implications of new science in evaluating formaldehyde leukemogenicity

Kenneth A. Mundt^{a,*}, P. Robinan Gentry^a, Linda D. Dell^a, Joseph V. Rodricks^a, Paolo Boffetta^b

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ABSTRACT

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde ("Draft IRIS Assessment"), also concluding that formaldehyde causes leukemia. Peer review of the Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" (NRC 2011). They offered recommendations for improving the Draft IRIS assessment and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key recommendations made by NRC and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

1. Introduction

Classification and regulation of human carcinogens is a key component to the protection and improvement of public health. However, proper regulation of industrial chemicals hinges on both valid hazard identification and quantitative risk assessment. Increasingly, hazard identification - at least where adequate scientific evidence is available draws on critically assessing and integrating evidence across lines of inquiry including animal and human toxicology (e.g., pharmacokinetic, mechanistic studies) and epidemiology. Quantitative risk assessment requires reasonably accurate characterization of exposure, which is complicated, especially where historical measures are sparse or do not exist. Where adequate evidence from some or all of these is lacking, and where important uncertainties remain, policy-driven approaches favoring precaution are warranted. On the other hand, as evidence accumulates, more science-focused methods can be employed, reducing uncertainties, leading to sounder conclusions. Nevertheless, confident conclusions are sometimes drawn prematurely, as discussed in this commentary. Recent evaluations of formaldehyde, coupled with improved critical review and evidence integration expectations and new, more focused scientific evaluations, illustrate the dynamic nature of scientific inquiry, the need for parallel refinement of hazard characterization, and subsequently, stronger risk assessment.

In this paper, we illustrate the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. The impetus for the new science summarized below is derived from the International Agency for Research on Cancer's (IARC) 2009 classification of formaldehyde as a known cause of leukemia in Monograph 100F (Baan et al., 2009; IARC, 2012), the US Environmental Protection Agency's (EPA's) similar classification in the *Draft IRIS (Integrated Risk Information System) Toxicological Review of Formaldehyde – Inhalation Assessment* (hereafter referred to as "Draft IRIS Assessment") (EPA, 2010), and the criticisms and recommendations presented in two National Academy of Science (NAS), National Research Council (NRC) expert reviews – one on the Draft IRIS Assessment and one on the IRIS process itself (NRC, 2011; NRC, 2014a). Various organizations and agencies have contributed to or sponsored the new science, including governments and universities, as well as industry. In revising and finalizing the Draft IRIS

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 ${\bf Table~1}\\ {\bf Summary~of~major~formaldehyde~carcinogenicity~classifications~and~noted~scientific~basis.}$

Year	Agency	Carcinogenicity Classification	Findings
1981	NTP (1981)	Anticipated to be a human carcinogen	Epidemiological evidence. Not discussed Toxicological evidence. One study cited (Swenberg et al., 1980). Nasal cancers: "While a full evaluation of the carcinogenicity of formaldehyde vapor must await completion of studies at the Chemical Industry Institute of Toxicology, evidence presented to date demonstrates that inhalation of formaldehyde results in a high incidence of nasal cancers in rats (Swenberg et al., 1980)."
1981 *	IARC (1982a; b)	Possibly carcinogenic to humans (Group 2B)	Epidemiological evidence. Inadequate (6 epidemiology studies) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to rat, causes nasal cancers.
1982	NTP (1982)	Anticipated to be a human carcinogen	Epidemiological evidence. Inadequate (cites IARC, 1982a; b) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to two strains of rats. Nasal cancers. One test in mice did not produce statistically significant results. Other studies in animals (mice and hamsters by inhalation exposure) were considered inadequate for evaluation.
1987 ^b	IARC (1987)	Probably carcinogenic to humans (Group 2A)	Epidemiological evidence. Limited Nasal cancers: Reported epidemiological evidence is strongest for nasal and nasopharyngeal cancer, noted limitations with small numbers of exposed cases and inconsistent reports. Leukemia: "Excess mortality from leukemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excess for these cancers among professionals is due to conditions other than formaldehyde. The slight excesses of cancer among professionals noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level, or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies." Toxicological evidence. Sufficient No changes in information reported from IARC (1982b) Supporting data. "In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings (IARC, Suppl
1991	EPA (1991)	Probable human carcinogen (Group B1)	6, 1987)." Epidemiological evidence. Limited (28 studies considered) Nasal cancers: "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products." (p.7) Leukemia: "Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated." (p. 8) Toxicological evidence. Sufficient, nasal squamous cell carcinomas Increased incidence of nasal squamous cell carcinomas observed in rats and mice in long-term inhalation studies. Supporting data. "The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as
1994 '	IARG (1995)	Probably carcinogenic to humans (Group 2A)	acetaldehyde." (p. 7) Epidemiological evidence. Limited Nasal cancers: Lack of consistency between cohort and case-control studies of cancers of the nasal cavities and paranasal sinuses. Leukemia: "The studies of industrial cohorts also showed low or no risk for lymphatic or hematopoietic cancers; however, the cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by a consistent lack of excess risk for brain cancer in the studies of industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists." (p. 334) Toxicological evidence. Sufficient (nasal squamous cell carcinomas) Squamous cell carcinomas of nasal cavities, at highest exposure. No evidence of carcinogenicity in hamsters. Mice showed no effect or were inadequate for evaluation. Supporting data. Genotoxic in variety of experimental systems in vivo. Induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, gene mutation in human and rodent cells in vitro. (continued on next page)



Table 1 (Table 1 (continued)					
Year	Agency	Carcinogenicity Classification	Findings			
2004 ³	IARC (2006)	Carcinogenic to humans (Group 1)	Epidemiological evidence. Sufficient, based on nasopharyngeal cancer Leukemia: "There is strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde. Increased risk for leukemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers." (p.276) Toxicological evidence. Sufficient (nasal squamous cell carcinoma) Supporting data. Mechanism for inducing myeloid leukema is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells. "The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of			
2009 "	IARG (2012)	Carcinogenic to humans (Group 1)	myeloid leukemia in humans." (p. 280) Epidemiological evidence. Formaldehyde causes cancer of the nasopharynx and leukemia. "The Working Group was not in full agreement on the evaluation of formaldehyde causing leukemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited." (p. 430) Toxicological evidence. "Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427) "Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p. 428) Inconsistent genotoxic effects in blood lymphocytes from animals exposed to formaldehyde via inhalation. Supporting data. "Particularly relevant to the discussions regarding sufficient evidence was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukeaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological prescursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430) "Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the			
2010	Draft IRIS Assessment (EPA, 2010)	Carcinogenic to humans	mechanisms is the most important." (p. 430) Epidemiological evidence. Sufficient. "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (p. 6–46). All LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts (embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (p. 4–180). All leukemias as a group: "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group." (p. 4–182) Myleoid leukemia: "Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Pinkerton et al., 2003; Hayes et al., 1990; Stroup et al., 1986; Walrath and Praumeri. 1984, 1983; but not Beane Freeman et al., 2009), the statistically significant meta-analysis by /bang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia. Four studies evaluated the leukemic formaldehyde exposure causes leukemia. Fou			



Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2012	NTP (2011)	Known to be a human carcinogen	Epidemiological evidence. Causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia." (p. 195) Toxicological evidence. No specific evidence cited regarding leukemia beyond the following: "Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these turmos were exposure-related, because of limitations in the reporting of these tumors (Soffritti et al., 2002)." (p. 198) Supporting data. "Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves, 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al., 2010a). Because formaldehyde is highly reactive and rapidly metabolized, a kely question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. The endogenous concentration does not increase after inhalation of formaldehyde from exogenous sources (Heck et al., 1985; Casanova et al., 1988; Heck and Casanova, 2004). Moreover, N2-hydroxymethyl-dG-DNA adducts have not be mediated at distal sites in rats (Such as the bone marrow,
2012	RAC (2012)	Carc. 1B - H50 ¹ May cause cancer	formaldehyde causes adverse haematological effects in humans." (p. 199) Epidemiological evidence. Limited "In conclusion, while some studies have found increased rates of leukemia, the epidemiology data do not show consistent findings across studies for leukemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukemia rates among embalmers, pathologist and anatomists, but not among industrial workers, suggests the possibility of confounding factors that bear investigation. Results based on cohort and case-control studies do not suggest an association between

tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumors in inhalation study of rats and mice (Kerns et al., 1983)." (p.22)

Supporting data. "Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found at values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde. These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as

the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic

Toxicological evidence. "No indication of carcinogenic potential on organs/

formaldehyde exposure and leukemia." (p.41)

effects are not found at anatomical sites distant from the port of entry." (p.44)

(continued on next page)



Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2016	Scientific Committee on Occupational Exposure Limits for Formaldehyde (Bolt et al., 2016)	Carcinogen Group C (genotoxic carcinogen with a mode- of-action based threshold)	Epidemiological evidence. Limited. Leukemias: "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45) Toxicological Evidence. "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49) Supporting Data. "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49)

[&]quot;IARC Working Group met February 1981. IARC Preamble (1982): "For many of the chemicals evaluated in the first 29 vol of the/ARC Monographs for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer."

- ^b IARC Working Group met March 1987.
- c IARC Working Group met October 1994; monograph published 1995.
- ^d IARC Working Group met June 2004; monograph published 2006.
- e IARC Working Group met October 2009; monograph published 2012.
- f EU harmonized classification and labelling.

Assessment (EPA, 2010), EPA now has the opportunity to incorporate the new evidence in addressing many of the issues raised by the NRC reviews.

2. Formaldehyde cancer hazard evaluation

The carcinogenicity of formaldehyde has been evaluated by several agencies since the early 1980s, including the IARC, the National Toxicology Program (NTP) of the National Institute for Environmental Health Sciences (NIEHS), the EPA, and most recently, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA), and the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission (Table 1). Except for the RAC review (RAC, 2012) and the SCOEL review (Bolt et al., 2016), which reclassified formaldehyde as a Carcinogen Category 1B (i.e., presumed to have carcinogenic potential for humans) and a Category C carcinogen (i.e., genotoxic carcinogen with a mode of action based threshold), respectively, these reviews classified formaldehyde as a known human carcinogen, primarily based on NPC but also on lymphohematopoietic malignancies (LHM) as a group and/or all leukemias as a group, and all myeloid leukemias (ML) as a group (EPA, 2010; IARC, 2012; NTP, 2011). Differences between NTP (2011) and EPA draft classifications (final version of the EPA review is pending) have been highlighted by Rhomberg (2015a) and differences between the IARC (2012) and the RAC (RAC, 2012) evaluations have been discussed by Marsh et al. (2014).

The reviews by authoritative bodies acknowledged that hazard identification for formaldehyde was not straightforward, especially with respect to possible leukemogenicity, in part due to its endogenous production and high reactivity. This prompted closer scrutiny regarding the methods used to critically evaluate the strength and quality of scientific studies, and ultimately, how best to integrate evidence across lines of inquiry such as animal, mechanistic and epidemiological evaluations.

IARC first classified formaldehyde as "carcinogenic to humans" (i.e., Group 1) in 2005 (Cogliano et al., 2005; IARC, 2006), revising the previous evaluation in 1995 that formaldehyde is "probably carcinogenic to humans" (i.e., Group 2A) (Table 1). The 2005 evaluation

(Cogliano et al., 2005; IARC, 2006) concluded that formaldehyde causes NPC, based primarily on results from animal studies, with additional evidence from "the largest and most informative cohort study of industrial workers" (i.e., Hauptmann, et al., 2004). Results from animal studies demonstrated that formaldehyde in direct contact with nasal passage tissues induced tumors at formaldehyde concentrations > 2 parts per million (ppm) as summarized by Nielsen et al. (2013) and later by Nielsen et al. (2017). This was considered consistent with formaldehyde's demonstrated genotoxicity, and with the "sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans" (IARC, 2006).

IARC (2012) concluded that formaldehyde also causes leukemia, and in particular ML, although the Working Group noted that it was a "small majority" who found the evidence to be sufficient. Neither Hauptmann et al. (2003) nor the subsequently updated study (Beane Freeman et al., 2009) published results specifically for acute myeloid leukemia (AML). The Working Group noted a study reporting aneuploidy in the blood of exposed workers (Zhang et al., 2010a), recently accepted for publication, provided supporting data, with the caveat that the study needed to be replicated (IARC, 2012). Indeed, proper replication of this study is still needed, because the study protocol was not consistent with adequate cell counting standards, including the authors' earlier descriptions of the OctoChrome FISH method (Zhang et al., 2005; Zhang et al., 2011) and other standards (American Society of Medical Genetics, 2006). One particular challenge is that occupational exposure limits in North America, Europe and in many countries around the world protect workers from the levels of occupational formaldehyde exposures that were studied by Zhang et al. (2010a) in China making replication of the study logistically difficult. Proper replication of this study also will require use of methods to successfully distinguish between aneuploidy arising in vivo from aneuploidy that arises during the period of in vitro culture, as discussed in section 3.3.3 below.

Following the IARC review and classification, the National Toxicology Program (NTP) concluded in the 12th Report on Carcinogens (12th RoC) that formaldehyde causes nasopharyngeal cancer and myeloid leukemia (NTP, 2011) (Table 1). The 12th RoC stated "The most informative studies for evaluation of the risk of ML are the large cohort studies of industrial workers (the NCI, NIOSH, and



British cohorts) and the NCI nested case-control study¹ of lymphohematopoietic cancer in embalmers" and specifically that "Three of these four studies found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships". However, the NTP also noted "In the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde exposure" and that in the only case-control study examining ML (Blair et al., 2000) "an excess risk was found for chronic (but not acute) myeloid leukemia" (NTP, RoC, 12th edition, "Formaldehyde", p.3).

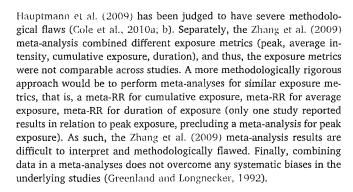
2.1. Environmental Protection Agency integrated risk assessment program (IRIS)

Formaldehyde had been classified by the EPA as a "probable" human carcinogen (Group B1) in 1991 (Table 1). An updated assessment for public review and comment was first released in June 2010, 12 years after the EPA announced the re-evaluation, and the draft assessment reported that formaldehyde causes NPC, nasal and paranasal cancer, lymphohematopoietic cancers, all leukemias, and ML (Table 1). The EPA (2010) also derived a draft inhalation unit risk (IUR) value of 8.1×10^{-2} per ppm $(6.6 \times 10^{-5} \text{ per } \mu\text{g/m}^3)^2$ based on the upper bound on the sum of the risk estimates for NPC, Hodgkin lymphoma, and leukemia (combined risks) based on part of the results reported in Beane Freeman et al. (2009). For rationale, the EPA said the classification "is supported by cohort analyses of embalmers, pathologists and anatomists (Hall et al., 1991; Hayes et al., 1990; Levine et al., 1984; Matanoski, 1989; Stroup et al., 1986; Walrath and Fraumeni, 1983, 1984)" despite the observation that "... SMR analyses of the large industrial cohorts do not indicate a similar association (Beane Freeman et al., 2009; Coggon et al., 2003; Pinkerton et al., 2004)" (EPA, 2010; page 4-180). The EPA also cited three meta-analyses (Bosetti et al., 2008; Collins and Lineker, 2004; Zhang et al., 2009) that largely included the same studies as providing additional evidence. Repeatedly reporting the same results, however, does not constitute independent or additional evidence. Similarly, all meta-analyses included earlier versions of the NCI cohort workers and embalmers studies and therefore, the meta-analyses, too, are redundant with the updated analyses of the NCI cohort workers and embalmers studies.

The conclusions in the Draft IRIS Assessment specific to myeloid leukemia are as follows:

"Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Hayes et al., 1990; Pinkerton et al., 2004; Stroup et al., 1986; Walrath and Fraumeni 1983, 1984; but not Beane Freeman et al., 2009), the statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia." (EPA, 2010; pages 4–184, 4–185)

Again, because of the significant overlap between Hauptmann et al. (2009) and the three PMR studies of funeral directors and embalmers (Hayes et al., 1990; Walrath and Fraumeni, 1983; 1984) these reports do not constitute independent evidence or consistency across studies.



2.2. National academies peer-review process

The NRC of the NAS, at the request of the EPA, formed an expert Committee to perform the peer-review of the Draft IRIS Assessment. Following a series of meetings during the second half of 2010, the NRC issued the final peer-review report on April 8, 2011 (NRC, 2011) as a pre-publication copy. The Committee identified numerous constructive criticisms and data gaps, and provided recommendations for improving IRIS reviews in general (NRC, 2011). Though not directly charged to evaluate the Draft IRIS Assessment conclusions, the peer review raised important questions regarding the underlying methods giving rise to several conclusions, including the basic causal conclusions:

"EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers—"all LHP cancers," "all leukemias," and "myeloid leukemias." The committee does not support the grouping of "all LHP cancers" because it combines many diverse cancers that are not closely related in etiology and cells of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas." (NRC, 2011; page 11)

The Committee concluded that EPA's claims that formaldehyde causes leukemia, ML or related hematopoietic cancers were not supported in EPA's assessment, appeared to be subjective in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion (NRC, 2011). The absence of such a framework was judged by the committee as problematic:

"As with the respiratory tract cancers, the draft IRIS assessment does not provide a clear framework for causal determinations. As a result, the conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data. Although EPA provided an exhaustive description of the studies and speculated extensively on possible modes of action, the causal determinations are not supported by the narrative provided in the draft IRIS assessment. Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to its conclusions." (NRC, 2011; page 11)

The NRC peer review further pointed out that the EPA (2010) conclusion that formaldehyde causes ML was based primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action) were not considered beyond studies conducted by Zhang et al. (2009, 2010a).

In the 7th and final chapter of its review, entitled, "A Roadmap for Revision," the NRC provided recommendations in two categories: "Critical Revisions of the Current Draft IRIS Assessment of



¹ This study technically is not a "nested case-control study" but rather a pooled reanalysis of death certificate data from several published proportionate mortality ratio (PMR) analyses, using a case-control approach. Thus, it carries the same limitations of death certificate analyses performed outside of a well enumerated cohort, and therefore is not "nested" in any true cohort that could be accurately enumerated.

 $^{^2}$ This is 15 times higher than the inhalation unit risk (IUR) derived by EPA for vinyl chloride (4.4 × 10⁻⁶ per µg/m³) (EPA, 2000; page 50), a chemical for which the evidence clearly supports a causal association between exposure and effects in both animals and humans.

Formaldehyde," and "Future Assessments and the IRIS Process" (NRC, 2011). NRC (2011) specifically identified the systematic review standards adopted by the Institute of Medicine (IOM), as being appropriate for such an analysis (IOM, 2011).

Following the release of the NRC (2011) peer review, Congress issued House Report No. 112–151 (US U.S. House, 2011), and directed EPA to incorporate recommendations of Chapter 7 of the NRC (2011) peer-review report into the IRIS process. In 2014, NRC released an additional report on the IRIS process (NRC, 2014a), and emphasized the importance of evidence integration for hazard identification, in which studies of higher quality and low risk of bias are given greater weight in drawing conclusions regarding causality.

As part of their response to the NRC reviews, the EPA convened a state-of-the-science workshop on formaldehyde on April 30 and May 1, 2014 in Arlington, Virginia. This workshop focused on three themes:

- Evidence pertaining to the influence of formaldehyde that is produced endogenously (by the body during normal biological processes) on the toxicity of inhaled formaldehyde, and implications for the health assessment:
- Mechanistic evidence relevant to formaldehyde inhalation exposure and lymphohematopoietic cancers (leukemia and lymphomas); and
- Epidemiological research examining the potential association between formaldehyde exposure and lymphohematopoietic cancers (leukemia and lymphomas).

(From: https://www.epa.gov/iris/formaldehyde-workshop)

A second workshop was announced at the meeting but never convened. Since then, the EPA submitted a progress report to Congress in 2015 (EPA, 2015) in response to a request from Congress (U.S. House, 2014, p. 59). Most recently, House Report No. 114–632 (U.S. House, 2016; page 57–59) and Senate Report No. 114–281 (U.S Senate, 2016; page 62) have requested the allocation of funds for NRC to peer review the revised IRIS Toxicological Review of Formaldehyde, to ensure that recommendations raised by the NRC (2011) were implemented.

3. New studies published since the 2011 NRC peer review of the draft IRIS assessment

Numerous studies and updated analyses have been published since the 2011 NRC peer review of the Draft IRIS Assessment, the findings of which, at least in part, fill many of the "data gaps" and address several key methodological issues highlighted in the NRC Committee recommendations (NRC, 2011). Below we summarize this new research, organized around the data streams (e.g., epidemiological, toxicological, and mode of action) for evidence integration and quantification of potential leukemia risks, specifically responsive to the following NRC recommendations (2011) (page reference provided):

• Epidemiological Evidence

- Discussion of the specific strengths, weaknesses and inconsistencies in several key studies, as the draft IRIS assessment relies solely on epidemiologic studies to determine causality. (p.113)
- Clarification of the basis of the EPA's interpretations of the Beane Freeman et al. (2009) results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (p.113)
- Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (p. 113)

• Toxicological Evidence

Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (p.110)

· Mode of Action Evidence

- Improving the understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (p. 58)
- Reconciliation of divergent statements regarding systemic delivery of formaldehyde, (p.59) as direct evidence of systemic delivery of formaldehyde is generally lacking. (p.5)
- Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (p. 5)

· Dose-Response Assessment

- Independent analyses of the dose-response models to confirm the degree to which the models fit the data appropriately. (p. 14)
- Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (p.14)
- Further justification of the selection and use of the NCI cohort (Beane Freeman et al., 2009) for calculation of unit risk because the cumulative exposure metric (used in the calculation of unit risk) was not related to leukemia risk in the NCI cohort. (p. 112)

· Methods for Evidence Integration

• Development of an approach to weight of evidence that includes "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (p. 113)

A summary of each of these recommendations and data gaps, along with the new science that has been conducted to address them is provided in Table 2 and discussed in the following sections.

3.1. Epidemiological evidence

The NRC peer review called attention to the EPA's sole reliance on epidemiological studies to determine causality, rather than integrating epidemiology data with the toxicological and mechanistic evidence. When inferring causation from epidemiology studies, the evidence is critically assessed and synthesized across a body of individual studies, with greater weight assigned to studies of higher quality (rather than assigning equal weight to each). Better epidemiological studies are those that implement individual level exposure data, and minimize the potential for systematic bias and confounding. The ascertainment of outcome and analysis using accurate (and specific) diagnosis are also critical in the causal evaluation. The NRC peer review noted that the grouping of "all LHPs" comprises 14 biologically distinct diagnoses in humans and should not be used in determinations of causality. There is some evidence that these diseases may originate from the same stem cell line (Gluzman et al., 2015; Goldstein, 2010) and could therefore arise from direct effects on these cells. There are no studies, however, that demonstrate an effect on these stem cells following exposure to formaldehyde. The largest population of these stem cells would be found in the bone marrow, and, based on the available evidence, inhaled formaldehyde appears incapable of reaching the bone marrow (see Section 3.3.2). The affected cells would need to be circulating stem cells that encounter formaldehyde at the portal of entry (i.e., the nose or upper airways) and then return to the bone marrow.

After the NRC peer review was published, Checkoway et al. (2012) critically reviewed the epidemiological evidence and reported inconsistent and sporadic associations between formaldehyde exposure and various specific LHM, including ML. Only a few epidemiology studies considered AML specifically. Since the critical review (Checkoway et al., 2012), several additional epidemiological studies have been published that provide insights on formaldehyde exposure and AML risk and address other specific issues raised by the 2011 NRC peer review. The key strengths and limitations of these studies are highlighted below.



Table 2 Summary of NRC (2011) comments or identified data gaps and new formaldehyde science by lines of inquiry.

NRC (2011) Comment/Identified Data Gap

New Formaldehyde Science

A. Epidemiological Evidence

- Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (NRC, p. 113)
- Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. (NRC, p. 113)
- Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (NRC, p. 112–113)
- The selection and use of the NCI cohort (Beane Freeman et al., 2009) should be further justified. (NRC, p. 112)

B. Toxicological Evidence

- Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (NRC, p. 110)
- C. Mode of Action Evidence
- Improve understanding of when exogenous formaldehyde exposure appreciably afters normal endogenous formaldehyde concentrations. (NRC, p. 58)
- Reconcile divergent statements regarding systemic delivery of formaldehyde (p.59); direct evidence of systemic delivery of formaldehyde is generally lacking. (NRC, p.5)
- Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (NRC, p. 5)

- Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. (NRC, p. 14)

- New analyses of the NCI formaldehyde workers cohort specifically for AML are reported.
 Results do not support the hypothesis that formaldehyde causes AML. See: Checkoway
 et al. 2015
- Associations seen between formaldehyde exposure and Hodgkin lymphoma and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. See: Checkoway et al., 2015
- A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoetic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation, See: Checkoway et al., 2012
- Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure, and few deaths occurred within 20 or more years of last peak exposure. Suggestive associations with peak exposure were observed for chronic myeloid leukemia, based on very small numbers. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (ptrend = 0.05) and peak (ptrend = 0.003) exposures. However, no other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. See: Checkovay et al., 2015
- Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941–2012. Results provide no support for an increased hazard of myeloid leukemia from formaldehyde exposure. See: Coggon et al., 2014
- Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results
 demonstrated limited evidence for formaldehyde exposure and any LHM including AML,
 based on 14 observed cases, See: Meyers et al., 2013
- No cases of leukemia or lymphohematopoietic neoplasia were seen. FA inhalation did not cause leukemia in genetically predisposed C3B6·129F1-Trp53tm1Brd mice. See: Morgan et al., 2017
- FA inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. See: Morgan et al., 2017
- Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake
 predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was
 predicted at lower exposure concentrations. See: Schroeter et al. (2014)
- With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. See: Yu et al., 2015
- Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. Also, new evidence suggests that endogenous formaldehyde in bone marrow is toxic and carcinogenic, and may cause leukemia (but not exogenous formaldehyde). See: Lai et al., 2016; Pontel et al., 2015; Yu et al., 2015; Edrissi et al., 2013; Moeller et al., 2011; fu et al., 2011.
- Critical review of the genotoxicity literature found no convincing evidence that exogenous
 exposures to FA alone, and by inhalation, induce mutations at sites distant from the portal
 of entry tissue as a direct DNA reactive mutagenic effect -- specifically, not in the bone
 marrow. Review of the existing studies of hematotoxicity, likewise, failed to demonstrate
 myelotoxicity in any species-- a probable prerequisite for leukemogenesis. See: Albertini
 and Kaden. 2016
- Reanalysis of selected raw data from the Zhang et al. (2010a) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect in vivo events, the reanalysis of the results provided by /hang et al. (2010a) raise sufficient questions that limit the use of Zhang et al. (2010a) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. See: Gentry et al. (2013)
- Additional analyses were performed on the study data obtained from the original study (Zhang et al., 2010a) including individual average formaldehyde exposure concentration measurements performed for each exposed worker. The objective was to evaluate haematological parameters and aneuploidy in relation to quantitative exposure measures of formaldehyde. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Furthermore, among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk. See: Mundt et al., 2017
- The documentation of the methods applied in the Draft IRIS Assessment (EPA, 2010) lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the NCI cohort study (Beane Freeman et al., 2009). This (continued on next page)



D. Dose-Response Assessment

Table 2 (continued)

NRC (2011) Comment/Identified Data Gap

New Formaldehyde Science

BBDR models developed by Conolly and co-workers should be used. (p.58) These models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. (NRC, p.57)

Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (NASNRC, p.14)

E. Methods for Evidence Integration

EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence." Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (NRC, p. 113)

- lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. See: Van Landingham et al., 2016
- Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. Work in progress: Clewell et al., unpublished
- Results of the "bottom-up" approach indicate that recent top-down risk extrapolations
 from occupational cohort mortality data for workers exposed to formaldehyde are overly
 conservative by substantial margins. See: Starr and Swenberg, 2013
- Updated "bottom-up" risk estimates heighten the marked contrasts that are present between
 the previous estimates and the corresponding USEPA estimates, with the larger difference
 for leukemia being due primarily to the significantly improved detection limit for the
 analytical method used in quantitating DNA adduct numbers. See: Start and Swenberg, 2016
- A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode-of-action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. See: Rhomberg et al., 2011
- Additional frameworks have been developed to integrate evidence. See: Adami et al., 2011; Lavelle et al., 2012; Lunkov et al., 2015; Rhomberg 2015b; Rooney et al., 2014; Woodruff and Sutton, 2014.
- Other agencies or advisory bodies have conducted assessments of the carcinogenicity of formaldehyde in a transparent manner. See: RAC, 2012; Bolt et al., 2016; Nielsen et al., 2017

3.1.1. Key studies and their strengths and limitations

Since the update of mortality in the US formaldehyde users and producers cohort (Beane Freeman et al., 2009), two other large industrywide cohort mortality studies have been updated: the NIOSH garment workers (Meyers et al., 2013) and the UK industry-wide formaldehyde producers and users (Coggon et al., 2014). In addition, a large population registry-based case-control study of incident AML cases in the Nordic countries, a small occupational study in Italy and a large multicenter European study of occupational exposures in a cohort established to study nutritional and metabolic risk factors in cancer risks have been published (Pira et al., 2014; Saberi Hosnijeh et al. 2013; Talibov et al., 2014).

3.1.1.1. NIOSH cohort study of garment workers. Meyers et al. (2013) updated mortality from 1960 through 2008 for 11,043 US garment workers exposed to formaldehyde who worked for at least three months between 1955 and 1983 at three US factories. A total of 36 leukemia deaths was reported (SMR = 1.04, 95% CI 0.73-1.44, compared to US mortality rates), of which 21 were ML (14 AML, 5 chronic myeloid leukemia (CML), 2 other and unspecified ML). Although this study did not link quantitative estimates of formaldehyde exposure to study subjects, an industrial hygiene survey during the early 1980s reported that formaldehyde concentrations were similar across all departments and facilities, and the overall geometric mean was 0.15 ppm with a geometric standard deviation of 1.90 (Stayner et al., 1988). The formaldehyde resins used to treat permanent press fabrics had been reformulated over time, and as a result, the formaldehyde concentrations measured in the early 1980s were believed to be lower than the approximately 4 ppm estimated by NRC for years prior to 1970 (NRC, 2014b). Meyers et al. (2013) reported an SMR for AML of 1.22 (95% CI 0.67-2.05), noting that NIOSH investigators "continue to see limited evidence of an association between formaldehyde and leukemia" and that "the extended follow-up did not strengthen previously observed associations." All 14 AML deaths occurred 20 or more years after first exposure to formaldehyde. The NIOSH study is a large cohort with adequate follow up but limited industrial hygiene measurements of historical formaldehyde concentrations, as most workers were first exposed prior to 1970. Therefore, the study did not assign individual estimates of cumulative or peak exposure, and analyses for mortality due to various LHM including AML were performed using duration of exposure as a proxy for cumulative exposure. Information on smoking was also lacking.

3.1.1.2. Registry-based case control study of AML in Nordic countries. Talibov et al. (2014) analyzed 15,332 incident cases of AML diagnosed in Finland, Norway, Sweden, and Iceland from 1961 to 2005. The investigators matched 76,660 controls to cases by year of birth, sex, and country. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (hazard ratio (HR) 0.89, 95% CI 0.81-0.97 for workers exposed to ≤0.171 ppm-years; HR 0.92, 95% CI 0.83-1.03 for workers exposed to 0.171-1.6 ppm-yrs, and HR 1.17, 95% CI 0.91-1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde). The strengths of this study were its exposure assessment based on a validatedJEM and the comprehensive ascertainment of incident AML cases (i.e., not deaths), resulting in high statistical power to detect increased risks, avoidance of survival bias, and the ability to consider and control for other possible leukemogens. One major limitation is the lack of data on smoking, which also is known to cause leukemia. This study failed to find an association between benzene and AML; however, increased risk of AML may be limited to those with exposure to very high concentrations that historically occurred only in a few occupational settings, e.g., the rubber hydrochloride industry (Infante et al., 1977; Schnatter et al., 2012).

3.1.1.3. European prospective investigation into cancer and nutrition (EPIC) cohort study. Saberi Hosnijeh et al. (2013) followed 241,465 subjects from 1992 through 2010 for a prospective study of lymphoid and myeloid leukemia risk in relation to occupation, nutrition and



metabolic risk factors. The European Prospective Investigation into Cancer (EPIC) investigators studied occupational risk factors among 477 incident leukemia cases (201 ML, including 113 AML, 237 lymphoid leukemia, and 39 other or unspecified leukemias) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy (Saberi Hosnijeh et al., 2013). Occupational exposures were estimated using a general population JEM that classified occupational codes of study subjects by categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). However, the authors reported that work histories were missing on a large number of cohort members, and these individuals had to be excluded. Study investigators lacked detailed job histories (job tasks and duration) for others, and the resulting exposure misclassification would be expected to be nondifferential, attenuating risk estimates. On the other hand, this is one of the few studies examining specific subtypes of leukemia with risk estimates adjusted for smoking and other risk factors. AML risk was not increased among the formaldehyde low-exposure group (HR 1.01, 95% CI 0.65-1.57) after adjusting for sex, smoking status, alcohol intake, age at recruitment and country, and no AML cases occurred among individuals in the high-exposure category. An HR for chronic lymphocytic leukemia of 1.45 (95% CI 0.46-4.56) was reported among those with high exposure to formaldehyde, but this was based on 3 or fewer cases. ML risks were increased among those employed in chemical laboratories and shoe and leather workers, and weakly increased among those exposed to benzene but not those exposed to ionizing radiation (Saberi Hosnijeh et al., 2013).

3.1.1.4. UK formaldehyde users and producers cohort study. Coggon et al. (2014) updated mortality through 2012 for the UK cohort of 14,008 formaldehyde users and producers; however, the analysis grouped all ML and did not analyze AML mortality separately. Similar to other large industrial cohorts (Beane Freeman et al., 2009; Meyers et al., 2013), industrial hygiene measurements were not available in the early years and investigators estimated averages for job titles based on irritant symptoms and later measurements. Exposures were estimated to range from background (< 0.1 ppm), low exposure (0.1-0.5 ppm), moderate exposure (0.6-2.0 ppm) and high exposure (> 2 ppm). These exposure categories were similar to those estimated by Stewart et al. (1986) and applied in Beane Freeman et al. (2009). Moreover, a larger proportion (and greater number) of the UK cohort was exposed to high concentrations of formaldehyde (approximately 18% of the cohort) than the US cohort (approximately 4% of the cohort). Coggon et al., 2014 reported no increased mortality from ML (SMR 1.16, 95% CI 0.60-2.20 for background exposure; SMR 1.46, 95% CI 0.84-2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450-1.82 for high exposure). In a nested case-control analysis of 45 ML (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was non-statistically significantly increased among workers exposed to high concentrations for < 1 year (OR 1.77, 95% CI 0.45-7.03), workers exposed to high concentrations ≥ 1 year showed no increased risk (OR 0.96, 95% CI 0.24-3.82) (Coggon et al., 2014).

3.1.1.5. Extended analysis of the NCI cohort study to evaluate specific types of myeloid leukemia. Checkoway et al. (2015) obtained the data from the NCI formaldehyde industrial workers cohort to further investigate specific types of leukemias, including AML (which had never been reported for this cohort), as well as performing an alternative analysis of peak exposure. The investigators reported that AML mortality was unrelated to cumulative exposure or peak exposure. Twelve of 34 AML deaths and 6 of 13 CML deaths occurred among study subjects with less than one year of employment. For workers employed at least one year, the risk of AML was highest (but not statistically significant) among workers with peak exposures of ≥2.0 to < 4 ppm (HR 1.78, 95% CI

0.61–5.25) and no trend was seen with increasing category of peak exposure (p for trend 0.37). In contrast, CML risks were greater, although the estimates were imprecise (HR 4.83, 95% CI 0.64–36.42 for peak exposure \geq 2.0 to < 4 ppm based on 2 CML deaths and HR 5.32, 95% CI 0.81–34.90 for peak exposure \geq 4 ppm based on 2 CML deaths).

3.1.2. Synthesis of epidemiology studies: exposure assessment issues identified by NRC

One of the major issues highlighted by the NRC peer review is that one exposure metric (peak exposure) was used to determine causality in the draft IRIS assessment, while a different exposure metric (cumulative exposure) was used for the dose-response evaluation to calculate an inhalation unit risk.

The NRC (2011) review of the Draft IRIS Assessment stated "the reliance on the peak exposure metric to determine causality rather than the more conventional dose metric of cumulative exposure should be further justified particularly in the absence of established modes of action" [p.112]. NRC further elaborated:

"In the absence of evidence regarding exposure-disease mechanisms, as in the case of formaldehyde and LHP cancers, cumulative exposure is typically the default dose metric applied in epidemiologic analyses and risk assessment. But the most significant results were found for peak exposures, which have the greatest associated uncertainty. In view of the importance of this study, EPA should clarify the basis of its interpretations of the results regarding the various dose metrics and the various LHP cancers. Despite those concerns, the committee agrees that the NCI study is the most appropriate available to carry forward for calculation of the unit risk." (NRC, 2011, pp. 112–113)

The NRC recommended that the quality of exposure assessment relied upon in epidemiological evaluations should be explicitly evaluated when weighting and synthesizing epidemiological evidence. Where known causal relationships have been observed, exposure-response relationships often are seen with various exposure metrics, with stronger associations seen when more relevant metrics and exposure time windows are examined. Results such as those reported by Beane Freeman et al. (2009) are a good example of conflicting findings: the conventional exposure metric, cumulative exposure, demonstrated no association with risk of ML, whereas a surrogate of 'peak' exposure suggested one (Beane Freeman et al., 2009). When evaluating differences between cumulative exposure and peak exposure, and comparing risks associated with these, several differences should be highlighted.

NCI investigators (Beane Freeman et al., 2009; Blair et al., 1986; Hauptmann et al., 2003) defined peak exposure as the maximum peak, and the NCI investigators substituted the time-weighted average (TWA) for jobs without assigned peak exposures (Stewart et al., 1986). The authors reported a significant test for trend between peak formaldehyde exposure and leukemia, but only when unexposed subjects were included. Increased risk was not seen for higher peak exposure categories (2.0 to < 4.0 ppm, or ≥ 4.0 ppm) when compared to the lower peak category (> 0 to < 2.0 ppm). No association was reported with frequency of peak exposure, average intensity of exposure or with cumulative exposure to formaldehyde ("There was little evidence among formaldehyde workers of association for any lymphohematopoietic malignancy (LHM) with average intensity or cumulative exposure at the end of follow-up in 2004." (Beane Freeman et al., 2009, p. 751). In fact, a 10% deficit of ML deaths (acute and chronic types combined) was reported when compared to US population mortality rates. In an internal analysis, Beane Freeman et al. (2009) reported that ML deaths were not associated with the number or frequency of peaks. If there were a true association between peak exposure and leukemia, one would expect to see an association with number of peaks and not only ever having a (perhaps single) peak exposure. Hauptmann et al. (2003) acknowledged that "no measurements of peak exposure were available



in this study. Peak exposures were therefore estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average" (Hauptmann et al., 2003, p. 1616; Stewart et al., 1986). Stewart et al. (1986) reported that the exposure reconstruction included rating confidence (i.e., confident, less confident, not confident) in the exposure estimate; however, the "confidence" category appeared to apply to the "rank" exposure and not the "peak exposure." For example, if an IH specified "not confident" for an average exposure estimate, it is not clear how or if this information applied to the estimate of peak exposure (categorized during data collection as 1 = none, 2 = 0.1–0.5, 3 = 0.51–2.0, 4 = 2.1–4.0, 5 = > 4.0, 9 = unknown) (Stewart et al., 1986).

In extended analyses of the NCI cohort study, Checkoway et al. (2015) refined the classification of peak exposure. Workers who did not work in jobs identified as likely having peak exposures were classified as not exposed to peaks, and became the referent group. A total of 3478 cohort members were classified as having worked in jobs with estimated peak exposure of 2- < 4 ppm, and 2907 worked in jobs with estimated peak exposure of ≥ 4 ppm. Analysis by ML subtype (i.e., AML and CML deaths, separately) found no association between peak exposure and AML mortality (HR 1.71, 95% CI 0.72-4.07 and HR 1.43, 95% CI 0.56-3.63, respectively) (Checkoway et al., 2015). However, 13 of the 34 AML deaths were classified as having worked in jobs likely having peak exposure > 2.0 ppm, only 4 of which worked in these jobs within the 20 years preceding their AML death (i.e., latest exposure), and only one occurred (similar to the number expected) within the typical AML latency window of 2-15 years. Upon fuller analyses of these data, Checkoway et al. (2015) subsequently found that only a third of all the AML deaths were among cohort members assigned to categories with any peak exposure (i.e., > 2.0 ppm), nearly all of whom had their last peak exposure more than 20 years earlier, well outside of the maximum latency window.

Coggon et al. (2014) also reported that limited IH data were available for the UK formaldehyde users and producers cohort, preventing the derivation of quantitative metrics. Nevertheless, the investigators expressed high confidence that the high exposure category corresponded to average concentrations of at least 2 ppm. Industrial hygiene data also were limited in the US NCI industrial workers study, although the investigators used them as part of a detailed exposure reconstruction using best practices for such a reconstruction at the time. Stewart et al. (1986) reported that historical exposure levels were estimated because most companies did not begin sampling until the mid-1970's: they also monitored "present day" (i.e., early 1980's) operations to help extrapolate historical exposures. The NCI investigators relied upon exposure rank (six levels of TWA): trace, < 0.1 ppm, 0.1–0.5 ppm, 0.51–2.0 ppm and > 2 ppm.

One criticism leveled at the UK worker cohort study (Acheson et al., 1984; Coggon et al., 2003, 2014; Gardner et al., 1993) was that the "authors reported a concern about the quality of data when they made exposure assignments" (NRC, 2014b). This criticism seems to stem from the appropriate identification and discussion of study limitations by earlier UK investigators: Gardner et al. (1993) reported "when jobs were being placed into qualitative categories of exposure in the British study, some disagreement occurred as to which of two adjacent grades was most appropriate-for example, high or moderate? To achieve consistency across all the factories, the higher of the two was always used. It is not clear how differences were resolved in the United States study." Thus, there are no essential differences in the approach used by the UK investigators and the US investigators: both studies reported that limited data were available on quantitative exposure measures using existing industrial hygiene data (from the 1980s); both exposure assessments allowed for the consideration of changes in processes and exposure controls during the period of the study; and both used ranked categories of exposure, developed before the estimation process, based somewhat on subjective sensory experiences encountered in the job (e.g., odor occasionally present), and both used eye irritation and odor throughout the day to identify the highest intensity of exposure jobs (Acheson et al., 1984; Stewart et al., 1986).

Ultimately, the Beane Freeman et al. (2009) study alone does not (and cannot) provide reliable support for a conclusion that peak formaldehyde exposure causes ML or AML, especially considering the absence of peak measurement data in the US study, the results of the reanalysis by Checkoway et al. (2015), and the updated results from the UK study (Coggon et al., 2014), which used a more conservative approach to exposure estimation.

3.1.3. Synthesis of epidemiology studies: evaluation of the most specific diagnosis

The NRC (2011) raised the issue that diverse types of leukemias and lymphomas should not be grouped "because it combines many diverse cancers that are not closely related in etiology and cells of origin. Although the draft IRIS assessment explores specific diagnoses—such as AML and CML, as well as Hodgkin lymphoma and multiple myeloma (see, for example, EPA 2010, Tables 4-92)—the determinations of causality are made for the heterogeneous groupings of "all LHP cancers," "all leukemias," and "ML". When results for heterogeneous groupings are presented, there is no evidence of increased risk of all LHP cancers (Meyers et al., 2013; Beane Freeman et al., 2009) or all leukemias combined (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009) in industrial cohorts when compared to general mortality rates. In addition, there is no evidence of exposure-response associations between all LHPs combined (or all leukemias combined) and cumulative exposure or average exposure (Beane Freeman et al., 2009) or duration of exposure (Meyers et al., 2013; Coggon et al., 2014).

Interestingly, the Draft IRIS Assessment noted that "Acute leukemias (ALL and AML), believed to arise from transformation of stem cells in the bone marrow, are less plausible. In contrast chronic lymphatic leukemia, lymphomas, multiple myelomas (from plasma B cells), and unspecified cancers may involve an etiology in peripheral tissues to include cells, cell aggregates, germinal centers, and lymph nodes. An association of these cancers to an exogenous agent acting at the POE [portal of entry] is biologically plausible" (EPA, 2010; page 4–190).

While the etiologies of most LHM are poorly understood, the possible role of environmental agents is plausible for AML, which has been linked with benzene, tobacco smoking, ionizing radiation and various cancer treatment agents, such as cisplastin, all of which have been classified by IARC as known human carcinogens that cause AML. It should be stressed that evidence exists that these agents, or their carcinogenic components, are capable of reaching the bone marrow. However, only six epidemiological studies of workers substantially exposed to formaldehyde published to date have published AML-specific results (Blair et al., 2001; Checkoway et al., 2015; Hauptmann et al., 2009; Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014), four of which were not available at the time of the IARC review or the release of the Draft IRIS Assessment. Saberi Hosnijeh et al. (2013) reported no association between "low" formaldehyde exposure and incidence of myeloid leukemia (HR 1.02, 95% CI 0.72-1.42 based on 49 cases exposed to formaldehyde and 130 unexposed cases). No differences were seen between subtypes: AML (HR 1.01, 95% CI 0.65-1.57) or CML (HR 0.92, 95% CI 0.46-1.84). No myeloid cases (and therefore no AML cases or CML cases) occurred among those classified as having "high" formaldehyde exposure (Saberi Hosnijeh et al., 2013). Talibov et al. (2014) found no association between formaldehyde and incident AML, after adjusting for exposure to specific solvents and ionizing radiation (HR 1.17, 95% CI 0.91-1.51 for 136 workers and 628 controls exposed to > 1.6 ppm-yrs). Meyers et al. (2013) reported a SMR for AML of 1.22 (95% CI 0.67-2.05) based on 14 observed AML deaths. Checkoway et al. (2015) performed AML-specific analysis using the NCI cohort, which had provided results only for all ML combined (Beane Freeman et al., 2009). When compared to US referent rates, AML mortality risk was decreased among workers



exposed to formaldehyde (SMR 0.80, 95 %CI 0.46–1.14) and internal analysis of exposure reported no trend with increasing cumulative exposure or peak exposure categories (Checkoway et al., 2015). Thus, new analyses of the NCI formaldehyde workers cohort specifically for AML detract from the hypothesis that formaldehyde causes AML.

The associations reported by Beane Freeman et al. (2009) between formaldehyde exposure and Hodgkin lymphoma and CML have not been observed in other studies (Meyers et al., 2013; Saberi Hosnijeh et al., 2013) and are less plausible, given the lack of known associations with Hodgkin lymphoma or CML and other chemicals or agents, such as benzene (Checkoway et al., 2015). Saberi Hosnijeh et al. (2013) reported a RR of 0.92 (95% 0.46 to 1.84) based on 46 CML cases. Meyers et al. (2013) reported a SMR of 1.35 (95% CI 0.44–3.15), based on 5 CML cases through 2008. The absence of established toxicological mechanisms for formaldehyde exposure and any of the LHM further weakens arguments for causation (Checkoway et al., 2012, 2015), especially given that inhaled formaldehyde appears incapable of reaching the bone marrow (discussed in Section 3.3).

3.2. Toxicological evidence

3.2.1. Animal evidence of formaldehyde-induced LHM

With regard to animal evidence of formaldehyde-induced LHM, the Draft IRIS Assessment (EPA, 2010) stated that the available animal evidence is limited, discussing mainly the results from the Battelle Columbus Laboratories (1981) study. The Draft IRIS assessment indicated that this study provides the only evidence of formaldehyde-induced LHM in animal models. However, the NRC (2011) peer review noted that although intriguing, EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981) contributed little to the weight of evidence evaluation.

In rats, Battelle Columbus Laboratories (1981) reported the incidence of leukemia (most of which were diagnosed as undifferentiated leukemia found sporadically in various organs) in male and female Fischer 344 rats following exposure to concentrations of 0, 2, 6, or 15 ppm for 24 months, followed by 6 months with no exposure. No concentration-related increases in the incidences of leukemia in either sex of rats were reported by Battelle Columbus Laboratories (1981), when a standard Fisher-Irwin exact test was applied (males $p=0.0972;\, females \, p=0.2316).$

Because of a significant number of early deaths in the high concentration group of both males and females, Battelle Columbus Laboratories (1981) also applied Tarone's extension to the Cox log-rank test (Tarone, 1975) to evaluate the leukemia incidence data. This test accounts for the number of animals at risk at each time point when the response of interest is observed. This adjustment assessed the probability of developing the endpoint of interest in those animals that did not survive until the termination of the study. The results of Tarone's extension indicated that the incidence among female rats in the high concentration group was statistically significant (p = 0.0056, not 0.0003 as reported3); however, no association was seen in the male rats exposed at high concentrations (p = 0.6891). No concentration-related increase in leukemia was observed in the female rats exposed at either 2 ppm or 6 ppm, and no survival problems were noted. Even after application of Tarone's extension, leukemia in male or female rats was not identified in the Battelle Columbus Laboratories (1981) study as an endpoint related to formaldehyde exposure, nor was it so designated in two publications citing this study (Kerns et al., 1983; Swenberg et al.,



More contemporary statistical methods, such as the Cochran-Armitage and the Poly3 (Bailer and Portier, 1988; Peddada and Kissling, 2006) trend tests, have replaced those used in the early 1980's. The Poly3 trend test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take inter-group survival differences into account. Importantly, the Poly3 test is the test currently used by the National Toxicology Program (NTP) to evaluate incidence data both for trend and pair-wise comparisons, to assess the probability of the response in the presence of inter-current mortality. The results of the application of these tests indicated p values of 0.43 and 0.82 for the Poly3 and Cochran-Armitage, respectively, demonstrating no association.

In mice, the Draft IRIS Assessment (EPA, 2010) suggested that the "adjusted" incidence of lymphoma in female mice, when the 6-month sacrifice animals were removed from consideration (because tissues outside of the respiratory tract were not examined), was statistically significant (p < 0.05) in animals exposed to 15 ppm formaldehyde, compared to untreated controls. However, as indicated in the methods for the Battelle Columbus Laboratories (1981) study, statistical significance, when applying the Tarone extension of the Cox test, is achieved with a p value of 0.05 divided by the number of dose groups. In the case of the Battelle Columbus Laboratories (1981) study for the mouse data, statistical significance would be p < 0.0167, as noted in the summary tables (Table 8 of the Battelle Columbus Laboratories (1981) report); therefore, based on this criterion, this endpoint was not considered statistically significant. As with the leukemia incidence in rats, the Battelle study authors did not report lymphoma in mice as an endpoint related to formaldehyde exposure.

Since 2010, two short-term carcinogenicity studies have been conducted and published (as a Technical Report) by the NTP of NIEHS in strains of genetically predisposed mice (male C3B6·129F1-Trp53tm1Brdp53 haplo-insufficient mice and male B6.129-Trp53tm1Brd) (Morgan et al., 2017). These short-term carcinogenicity studies were conducted to test the hypothesis that formaldehyde inhalation would result in an increased incidence and/or shortened latency to nasal and lymphohematopoietic tumors and to investigate hypotheses that formaldehyde may induce leukemia by a mechanism not involving DNA adduct formation. This proposed mechanism assumes that inhaled FA could cause significant genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. These damaged stem cells could reach the general circulation, home to tissues that support the hematopoietic niche, undergo lodgement and become leukemic stem cells. The animals were exposed to 7.5 or 15 ppm formaldehyde 6 hours/day, 5 days/week, for 8 weeks. The investigators reported that because the doubling time for hematopoietic stem and progenitor cells (HSPCs) is between 2 and 4 weeks, and the entire HSPC pool turns over every 8 weeks, an 8 week exposure duration was considered sufficient to investigate the hypothesized mechanism for inducing leukemia. Following the 8-week inhalation exposure, mice were monitored for approximately 32 weeks (until approximately 50 weeks of age). At the highest concentrations, significant cell proliferation and squamous metaplasia of the nasal epithelium were observed; however, no nasal tumors were observed. No cases of leukemia were seen in either strain and a low incidence of lymphoma in exposed mice was not considered related to exposure. In addition, no significant changes in haematological parameters were noted. Under the conditions of these studies, the authors concluded that formaldehyde inhalation did not cause leukemia in these strains of genetically predisposed mice (Morgan et al., 2017).

Overall, the weight of evidence from animal studies reported in the Draft IRIS Assessment (EPA, 2010) did not support an association between formaldehyde exposure and LHM. Since that time, additional studies (Morgan et al., 2017) have provided evidence that suggests a lack of association between formaldehyde exposure and LHM. In addition, no evidence of changes in blood parameters that might be



³ This appears to be a misreading of the Battelle report. In the Battelle Report Volume A Table 10 – Analysis of Effects of Formaldehyde in Female Rats - reports a p-value of 0.0056 from the Adjusted Cox/Tarone pair-wise comparison of the control to 15 ppm for Leukemia, all. The next row in that table with an endpoint of Uterus, Endometrial Stromal Polyp is the one that reports a p-value of 0.0003 for the pair-wise analysis of control to 15 ppm.

associated with leukemias has been reported in any animal studies exposed to formaldehyde at high concentrations following both acute and chronic durations (Appelman et al., 1988; Dean et al., 1984; Johannsen et al., 1986; Kamata et al., 1997; Kerns et al., 1983; Til et al., 1988, 1989; Tobe et al., 1989; Vargova et al. 1993; Woutersen et al., 1987). Among these studies, Vargova et al. (1993) reported *increased* red blood cell counts and *increased* proportions of lymphocytes and monocytes in rats, rather than decreases, following exposure to formaldehyde by gavage at 80 mg/kg/day for 28 days.

3.3. Mode of Action Evidence

3.3.1. Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations

NRC (2011) recommended that one key improvement to the science would be an understanding of when exogenous formaldehyde exposure altered normal endogenous formaldehyde concentrations. Because formaldehyde is endogenously present, it is important to differentiate levels that are due to normal metabolic processes from levels that might be present as a result of exogenous exposure. A number of studies have applied sensitive methods to differentiate exogenous and endogenous levels of formaldehyde in tissues (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011).

The results of these studies with highly sensitive instruments and accurate assays indicate that inhaled formaldehyde was present in the nasal respiratory epithelium, but not other tissues beyond the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively (Yu et al., 2015).

An additional study conducted in rats exposed to 13C-formaldehyde (Kleinnijenhuis et al., 2013) provided results consistent with those from studies focused on measuring endogenous versus exogenous DNA adducts. In this study, Sprague-Dawley rats were exposed nose-only to 10 ppm $^{13}\text{C-formaldehyde}$ for 6 hours and blood concentrations evaluated during exposure and for 30 minutes following exposure. This study was conducted specifically to investigate the mechanism proposed by Zhang et al. (2010a) that formaldehyde is absorbed during respiration and could reach any target tissue, such as the bone marrow, via the blood in the form of methanediol to exert its genotoxic activity. Exogenous 13C-formaldehyde was not detectable in the blood of rats either during or up to 30 min after the exposure. The authors concluded that "it is highly unlikely that the mechanism proposed by Zhang et al. (2009), that exposure to FA by inhalation may lead to an increased FA concentration in blood and as such may cause leukemia, is true" (Kleinnijenhuis et al., 2013).

New studies have been conducted to investigate the potential toxicity/carcinogenicity of endogenous formaldehyde. The most recent studies demonstrate that endogenous formaldehyde in bone marrow is toxic, and probably carcinogenic, and therefore may increase leukemia risk (Pontel et al., 2015; Lai et al., 2016).

3.3.2. Reconcile divergent statements regarding systemic delivery

Multiple studies in rats (Lu et al., 2011; Yu et al., 2015; Edrissi et al., 2013) and monkeys (Moeller et al., 2011; Yu et al., 2015) conducted with sensitive analytical methods that can measure endogenous versus exogenous formaldehyde DNA or protein adducts have demonstrated that inhaled exogenous formaldehyde is not systemically absorbed or reaches sites distant from the point of initial contact. In addition to these studies, the available data on the toxicokinetics of formaldehyde suggest that no significant amount of "free" formaldehyde would be transported beyond the portal of entry.

In addition to studies supporting the lack of systemic delivery of formaldehyde, anatomically accurate computational fluid dynamics (CFD) models of the rat, monkey, and human have been applied to evaluate the effects of endogenously present formaldehyde on uptake from the respiratory tract. The consideration of endogenous formaldehyde concentrations in nasal tissues did not affect flux or nasal uptake predictions at exposure concentrations > 500 parts per billion (ppb); however, reduced nasal uptake was predicted at lower exposure concentrations (Schroeter et al., 2014).

3.3.3. Data are insufficient to conclude formaldehyde is causing cytogenetic effects at distant sites

The modes of action that have been proposed in the Draft IRIS Assessment (EPA, 2010) to cause leukemogenesis rely strongly on the hypothesis that exposure to inhaled formaldehyde can result in cytogenetic effects at sites distant from the portal of entry. While the NRC (2011) noted that numerous studies have shown genotoxic effects in cells exposed *in vitro*, and a few studies have shown positive cytogenetic effects in circulating blood lymphocytes in heavily-exposed workers, they also noted that it is unlikely that these effects are relevant to a possible leukemogenic effect of formaldehyde, particularly at low exposure levels. The potential leukemogenic effect and exposure-response relationships at lower exposure levels have been comprehensively evaluated by Nielsen et al. (2013, 2017).

One key study cited in multiple agency evaluations as providing evidence of cytogenetic events in the development of leukemias is by Zhang et al. (2010a, 2010b) compared the prevalence of markers of hematopoietic function and chromosomal aneuploidy among workers occupationally exposed to formaldehyde with those of a group of unexposed workers in China, Ninety-four workers were included, with 43 workers occupationally exposed to formaldehyde and 51 workers unexposed to formaldehyde as controls. The authors reported a higher prevalence of monosomy 7 (loss of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures of CFU-GM colony cells. The authors suggested that this demonstrated that formaldehyde exposure was associated with an increase in leukemiaspecific chromosomal aneuploidy in vivo in the hematopoietic progenitor cells of the exposed workers. However, no direct in vivo metaphases had been examined in workers blood. Furthermore, this was a cross-sectional comparison of blood and cytogenetic measures between two groups, and observed differences could not be established as resulting from formaldehyde exposure or due to other overall differences between the two groups.

Two re-analyses of the underlying data from the Zhang et al. (2010a) study have been published (Gentry et al., 2013; Mundt et al., 2017). The first (Gentry et al., 2013) relied upon selected underlying data provided through a Freedom of Information Act request that included: 1) individual data on blood cell counts in both formaldehydeexposed and unexposed individuals including any data on health status of these individuals; 2) individual data on the FISH results for monosomy 7 and trisomy 8 for cultures of samples obtained from 10 formaldehyde-exposed workers and 12 unexposed controls; 3) data on additional chromosomal abnormalities examined and/or observed; and 4) details of the methods sufficient for a qualified scientist to replicate the results reported in the Zhang et al. (2010) study. The results of this reanalysis suggested that factors other than formaldehyde exposure likely contributed to the reported findings. In addition, although the authors stated in their paper that "all scorable metaphase spreads on each slide were analyzed, and a minimum of 150 cells per subject was scored," this protocol was not followed specifically for chromosome 7 or chromosome 8 (recent correspondence indicates a minimum of 150 total metaphases were scored for 24 chromosomes per subject). Far too few cells were counted to draw any meaningful conclusions, and far fewer than the approximately 400 per chromosome cited in previous analyses in which the protocol was described (Zhang et al., 2005, 2011). In addition, the assays used (CFU-GM) do not actually measure the proposed events in primitive cells involved in the development of AML. Evaluation of these data indicates that the aneuploidy measured



could not have arisen in vivo, but rather arose during in vitro culture.

In 2014, Mundt et al. requested the individual exposure measurement data for each of the participants in the Zhang et al. (2010a) study from NCI. In 2016, the request was in part granted and the mean formaldehyde estimate for each exposed worker (but not the individual exposure measurement values) was provided via a Technology Transfer Agreement (TTA) with NCI. Using these data, the Gentry et al. (2013) reanalysis was extended to include exposure-response analyses. Results of this second reanalysis showed that differences seen at the group comparison level, i.e., comparing the prevalence of white blood cell, granulocyte, platelet, and red blood cell counts at the group level in fact were independent of measured formaldehyde exposure level. Among exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of ML risk. Differences between the two groups of workers, other than formaldehyde exposure, were therefore likely to explain the results reported by Zhang et al. (2010a).

Subsequent studies of the same population of formaldehyde-exposed and non-exposed workers in China (Lan et al., 2015; Seow et al., 2015; Bassig et al., 2016) have been suggested by the authors to confirm the results of Zhang et al. (2010a); however, many of these studies report results from the same biological samples as Zhang et al. (2010a) and therefore, do not provide replication of the results. The repeated use of the original Zhang et al. (2010a) data, and its implications, have been reiterated (Pira et al., 2017; Gentry et al., 2013; Speit et al., 2010) and the original authors have responded to some of the criticisms (Rothman et al., 2017; Lan et al., 2015; Zhang et al., 2010b). Replication of the Zhang et al. (2010a) results will require replication in an independent population of formaldehyde-exposed workers, and where methodological issues are adequately addressed. An attempt to replicate the results could be conducted in the same population of workers as Zhang et al. (2010a) and Lan et al. (2015) in which the median exposures to 43 workers were 1.28 ppm (10th and 90th percentile: 0.63, 2.51 ppm). However, as noted previously (Section 3.1.1), no evidence of an association between formaldehyde exposure and leukemias has been reported in multiple recent epidemiological studies with large numbers of subjects that have been exposed to concentrations > 2.0 ppm. The increasing evidence that inhaled formaldehyde does not move beyond the portal of entry (Section 3.3.2) also calls into question many of the conclusions from Zhang et al. (2010a).

Albertini and Kaden (2016) reviewed the body of data that reportedly indicates genetic changes in circulating blood cells and in blood-borne hematopoietic precursor cells (HPCs). These changes have been considered to be indicators that systemic genotoxicity occurs after human inhalation exposure to formaldehyde, although the mechanisms by which this could occur remain unknown. For each study, the authors examined the sources of exposure, possible co-exposures, biomarkers for internal exposures and genetic signatures of formaldehyde effects.

In reviewing the available studies, many genetic changes in blood cells were noted by Albertini and Kaden (2016), with a contrast in results between animal and human studies: the majority of animal studies were negative and the majority of human studies were positive. This pattern was attributed to the difference in target cell being studied, with bone marrow cells studied in animals and peripheral blood lymphocytes studied in humans. Exposure of human cells to formaldehyde at sites of contact in vivo could provide opportunities for exposure of Tlymphocytes to formaldehyde or products of oxidative stress, which could result in the genetic changes observed in peripheral blood cells. However, these results are inconsistent with results from controlled animal studies, discussed previously, that demonstrate - by labeling administered formaldehyde - inhaled (exogenous) formaldehyde does not travel beyond the portal of entry (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011). Therefore, these types of genetic changes reported in human studies do not provide evidence that formaldehyde moves beyond the portal of entry to the bone marrow, which would be necessary to result in direct induction of chromosome-level mutations in the bone marrow. Despite the apparent inability of exogenous formaldehyde to reach the bone marrow, the mutagenic effects of formaldehyde in bone marrow have not been tested in humans.

Albertini and Kaden (2016) concluded that overall, the available literature on genetic changes following formaldehyde exposure did not provide convincing evidence that exogenous exposure, and specifically exposure by inhalation, induces mutations as a direct DNA-reactive effect at sites distant from the portal-of-entry tissue. This would include proposed mode of actions that involve a stem cell effect at the portal of entry with circulation back to the bone marrow. Such exposures have not been shown to induce mutations in the bone marrow or in any other tissues beyond the point of contact. Thus, the weight of scientific evidence does not provide biological plausibility of lymphohematopoietic cancers, as proposed by EPA (2010) and NTP (2011).

3.4. Dose-response assessment

Several NRC (2011) peer-review comments were raised regarding the dose-response assessment conducted by EPA in the Draft IRIS Assessment (2010). One comment highlighted the need to conduct independent analyses of the dose-response models, using the data from the Beane Freeman et al. (2009) study to confirm which models fit the data appropriately (NRC, 2011). Using the original data from the key study (Beane Freeman et al., 2009) and documentation provided in the Draft IRIS Assessment, Van Landingham et al. (2016) attempted to duplicate the reported inhalation unit risk (IUR) values for Hodgkin lymphoma and all leukemias and address the NRC Committee's questions regarding application of the appropriate dose-response model. Overall, there was difficulty duplicating the IURs reported by EPA (2010), largely due to a lack of critical information provided in the IRIS documentation. Perhaps most problematic, the first step of the analysis did not determine significant exposure-response relationships between formaldehyde and lymphohematopoietic endpoints for the metric (cumulative exposure) needed in the estimation of an IUR. The authors concluded that the resulting analysis, while it could be mechanically performed, provided no valid or useful insights on the risks of formaldehyde exposure. The lack of apparent exposure-response relationships for selected endpoints raises the question whether quantitative analyses are appropriate for these endpoints, and if so, how results are to be interpreted.

The NRC (2011) also noted the need to consider alternative extrapolation models for analyzing the cancer data. In 2013, Starr and Swenberg proposed a novel "bottom-up" approach for bounding lowdose human cancer risks using formaldehyde as an example (Starr and Swenberg, 2013). This approach requires information on background risk, background or endogenous exposure and the additional exogenous exposure of interest. The results of this approach provided estimates of risk ($< 3.9 \times 10^{-6}$) that were more than 14,000-fold lower than the corresponding Draft IRIS Assessment (EPA, 2010) estimate for all leukemias (5.7 \times 10⁻²) and considers the impact of background endogenous formaldehyde concentrations, which is not considered in the Draft IRIS Assessment (EPA, 2010). In 2016, Starr and Swenberg provided an update to this approach, incorporating new formaldehyde-DNA adduct data, and allowing for uncertainty in two of the parameters (background cancer risk and background endogenous concentrations of formaldehyde) (Starr and Swenberg, 2016). Consideration of the statistical uncertainty in these two parameters resulted in estimates of risk for leukemias that were even smaller than those initially estimated in Starr and Swenberg (2013). The authors concluded that these estimates provide a reality check for the IUR presented in the Draft IRIS Assessment (EPA, 2010). In addition, the large discrepancy between results using an approach that relies on molecular dosimetry data (i.e., the bottom up approach) versus one that relies upon uncertain retrospective occupational exposure reconstructions (i.e., the approach



relied upon in EPA (2010) call into question the credibility of attributing increases in human mortality from leukemias to occupational exposure to formaldehyde.

3.5. Methods for evidence integration

The NRC (2011) noted that the Draft IRIS Assessment's (EPA, 2010) approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version.

Since the Draft IRIS Assessment (EPA, 2010) and the NRC (2011) peer review, several frameworks have been developed to integrate evidence across different lines of scientific inquiry including epidemiology, toxicology and mode of action studies (Adami et al., 2011; Lavelle et al., 2012; Linkov et al., 2015; Rhomberg, 2015b; Rooney et al., 2014; Woodruff and Sutton, 2014). The EPA has also proposed preliminary approaches for integrating evidence in response to the NRC (2011) peer review of formaldehyde (EPA, 2013a).

Rhomberg et al. (2011) applied a hypothesis-based weight of evidence approach to evaluate formaldehyde and leukemogenesis, considering how human, animal and mode of action results inform one another. In comparing the potential alternative proposals for causality, the authors concluded that the evidence for a causal association between formaldehyde exposure and leukemia is not only weak but strains biological plausibility (Rhomberg et al., 2011).

Nielsen et al. (2017) also considered the body of formaldehyde research while re-evaluating the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Nielsen et al. (2017) iterated that although formaldehyde is genotoxic and causes DNA adduct formation, it is also clastogenic. Exposure-response relationships from both animal and human data were nonlinear, and relevant genetic polymorphisms had not been identified. Although one epidemiological study had reported an association with nasopharyngeal cancer and others reported inconsistent associations with leukemias, relative risks were not increased below 1 ppm (mean exposures). Because inhaled formaldehyde does not pass beyond the respiratory epithelium, any direct effects are limited to portal-of-entry effects (Nielsen et al., 2017).

Other reviews and syntheses of evidence focused on epidemiological studies, and this body of literature has been most variably interpreted. In 2014, an independent National Research Council committee was charged with performing a peer review of the NTP evaluation of formaldehyde for the 12th edition of the RoC (NRC, 2014b). This NRC committee produced a new definition for "sufficient evidence" of carcinogenicity as demonstrated by two or more strong or moderately strong epidemiological studies with different study designs and populations showing associations between formaldehyde exposure and a specific cancer type. In this approach, "strong" epidemiology studies do not refer to the magnitude of the association, but relect a judgment of study quality and utility made by reviewers who considered chance, bias, and confounding as alternative explanations for the observed association and found these were not reasonable explanations. Further, "strong" epidemiology studies comprised large populations with long durations of exposure and an adequate follow up period to allow for latency, and had exposure assessments that were able to discriminate between "high" and "low" formaldehyde exposure categories. This "strength of evidence" approach contrasts with a "weight of evidence approach." Although each epidemiology study was classified as one of three categories (strong, moderately strong, or weak), this approach suggests that 2 or more strong or moderately strong studies with positive results are enough to conclude sufficient evidence of carcinogenicity exists, and discounts epidemiology and animal studies that are negative or contradictory.

Meta-analyses are often used to synthesize findings across many

epidemiology studies, identifying sources of potential heterogeneity which then can be explored in interpreting the overall evidence. In the Draft IRIS Assessment (EPA, 2010), meta-analyses conducted by several investigators were considered (Zhang et al., 2009; Collins and Lineker, 2004; Bosetti et al., 2008). Since then, two additional meta-analyses were conducted (Bachand et al., 2010; Schwilk et al., 2010). Bachand et al. (2010) excluded lower-quality studies and reported a meta-RR of 1.05 (95% CI 0.93-1.20) based on 16 cohort studies and a meta-OR of 0.99 (95% CI 0.71-1.37) based on 2 case-control studies for all leukemia, reported separately due to heterogeneity. Schwilk et al. (2010) published a meta-analysis of the epidemiological findings on myeloid leukemia, but limited to the highest-exposed sub-group reported in four studies (three cohort and one case-control): RR = 2.47; 95% CI, 1.42 to 4.27. Checkoway et al. (2012) conducted a critical review and synthesis of the epidemiological evidence and concluded that results from epidemiological studies were not consistent and did not show strong results or exposure-response associations. None of these reviews, however, included the results from the extended follow up of the NIOSH garment workers study (Meyers et al., 2013), the extended follow up of the UK producers and users (Coggon et al., 2014) or the extended analyses of the NCI cohort (Checkoway et al., 2015). In addition, metaanalyses and/or critical reviews of epidemiological literature require further integration with other lines of evidence.

4. Conclusions

It has been seven years since the release of the Draft IRIS Toxicological Review of Formaldehyde (EPA, 2010). In peer-reviewing this draft report, an NRC Committee raised many substantive questions related specifically to the conclusions drawn in the document and the quantitative estimates of potential toxicity (NRC, 2011). This Committee was tasked with reviewing and commenting on information provided in the draft assessment, and did not independently conduct a review of the primary literature, but did determine that many of EPA's conclusions were not supported by the information and studies cited in the draft assessment. The committee also identified general methodologic problems with the Draft IRIS Assessment, and provided specific comments related to the evaluation of specific studies and conclusions based on the available evidence. The comments related to a causal association between formaldehyde exposure and LHM largely involved the interpretation of the available evidence at that time and the framework in which it was evaluated by EPA (2010). The committee found that EPA's preliminary conclusion that formaldehyde causes leukemia, ML or related hematopoietic cancers appeared to be "subjective' in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The absence of such a framework was judged by the committee as troublesome, given that the scientific evidence on the question was weak (NRC, 2011).

Since the NRC (2011) peer review, significant additional scientific evidence has become available that addresses many of the questions raised by the NRC Committee regarding a causal association between formaldehyde exposure and LHM. Some of these new studies and analyses were conducted in response to the NRC (2011) comments and recommendations, while others reflect ongoing work and updates of studies on this topic. All add to the scientific evidence surrounding the potential causal relationship between formaldehyde inhalation exposure and LHM, and should be addressed in the critical evaluations and integration of evidence presented in an updated IRIS Assessment.

Also since the NRC (2011) peer review, the EPA has proposed enhancements to the IRIS process (EPA, 2013b) that incorporate many of the general recommendations made by the NRC (2011) related to methodological issues. This process involves the evaluation and synthesis of evidence within separate streams of evidence (human, animal and mechanistic). However, in a critical review of the process conducted by a separate NRC Committee, while there was improvement in guidelines for evaluation and synthesis of evidence within an



evidence stream, the NRC Committee still noted limitations in synthesizing or integrating evidence across streams or categories (NRC, 2014a).

Nearly all of the recently available evidence from multiple lines of evidence, especially those studies that have been focused on addressing comments from the NRC Committee reviewing the Draft IRIS Assessment (NRC, 2011), have increased the weight of evidence favoring a conclusion of a lack of a causal association between formaldehyde exposure and LHM. The Checkoway et al. (2015) re-analysis using the data from the Beane Freeman et al. (2009) study was able to address directly several questions and comments from the NRC (2011) Committee, as the Draft IRIS Assessment (2010) was highly dependent on this study for drawing both qualitative and quantitative conclusions related to formaldehyde leukemogenicity and risk of LHM following inhalation exposure to formaldehyde. The Checkoway et al. (2015) reanalysis provides several results and insights relevant for assessing the risk of specific LHM. Not the least of these, the AML-specific results provide no support for the conclusion that formaldehyde causes AML. Associations seen between formaldehyde exposure and Hodgkin lymphoma and CML are inconsistent with other studies and also lack a plausible biological mechanism (Checkoway et al., 2015). NTP (2011) also noted that because the evidence for Hodgkin lymphoma is mainly limited to the NCI cohort study, a causal association cannot be established. No other LHM was associated with either cumulative or peak formaldehyde exposure. These results of the fuller analysis of the data from Beane Freeman et al. (2009) are consistent with recent epidemiological studies (Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014) which report no significant increase in LHM, specifically AML, among cohorts of workers exposed to formaldehyde.

The available animal evidence did not support a causal association between formaldehyde exposure and LHM at the time the Draft IRIS Assessment (EPA, 2010) was released. Since that time, additional studies have been conducted by the NTP using two sensitive assays in mice genetically predisposed to develop cancer following short-term exposure to a chemical (Morgan et al., 2017). These studies provided no evidence of changes in endpoints related to LHM or the presence of any LHM following exposure to high concentrations (15 ppm) of formaldehyde.

Studies conducted to evaluate potential mechanisms associated with formaldehyde exposure and LHM have demonstrated a lack of evidence for exogenous formaldehyde to move beyond the portal of entry. Multiple studies conducted in multiple species using highly sensitive techniques (Edrissi et al., 2013; Lu et al., 2011; Moeller et al., 2011; Yu et al., 2015) have demonstrated that while endogenous formaldehyde is present in all tissues, exogenous formaldehyde following inhalation exposure is not transported systemically. While some mechanisms for the development of LHM following inhalation exposure to formaldehyde have been hypothesized (EPA, 2010; Zhang et al., 2009, 2010a), there is no evidence to support these proposed mechanisms and the NRC Committee noted that:

"Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures." (NRC, 2011; page 45)

The more recent research all but confirms this. Several modes of action have been proposed, relying primarily on data reported by Zhang et al. (2010a) as well as subsequent evaluations of the same population of Chinese workers (Bassig et al., 2016; Lan et al., 2015; Seow et al., 2015). These include a mode of action in which risk of ML is increased due to immune suppression resulting from formaldehyde exposure (Bassig et al., 2016; Seow et al., 2015). The speculated modes of action,

however, assume systemic delivery of formaldehyde except one, which is a hypothesized mode of action in which hematopoietic cells in the nasal epithelium that are impacted by exposure to formaldehyde return to the bone marrow. The NRC Committee considered this proposed mode of action and concluded that:

"As a result, EPA could only speculate that circulating hematopoietic stem cells that percolate through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for mutations and clastogenic effects that eventually result in lymphohemotopoletic cancers. Experimental evidence of [this] mechanism is lacking." (NRC, 2011; page 45)

This currently leaves no acceptable proposed mode of action for the development of LHM following inhalation exposure to formaldehyde that can be scientifically substantiated.

The available toxicokinetic data also do not support the transport of inhaled formaldehyde from the portal of entry. The studies by Swenberg and colleagues unequivocally demonstrate that exogenous formaldehyde exposure does not increase formaldehyde concentrations measured in any internal tissues over those in unexposed animals, i.e., endogenously produced formaldehyde is the predominant if not only source of internal formaldehyde (Edrissi et al., 2013; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011; Yu et al., 2015).

The biological plausibility of a mode of action for the development of LHM following inhalation exposure to formaldehyde has relied heavily upon the incompletely reported results from the Zhang et al. (2010a) study in which the authors report differences between groups of formaldehyde exposed and unexposed groups in the frequency of monosomy 7 (loss of chromosome) and trisomy 8 (gain of chromosome), based on metaphase spreads prepared from culture of CFU-GM colony cells. However, reanalysis of the underlying raw data in two studies (Gentry et al., 2013; Mundt et al., 2017) have identified methodological problems with this study that challenge these conclusions, as well as demonstrate a lack of association between level of formaldehyde exposure and the observed aneuploidy (or any of the haematological measures).

Overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of LHM has increased substantially since the completion of the Draft IRIS Assessment (EPA, 2010) and release of the NRC peer review (NRC, 2011). New evidence has been published in each of the major streams of evidence (i.e., human, animal and mechanistic) that consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the NRC (2011) scientific criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure. Regardless of which of the several similar approaches to integrating the available evidence between formaldehyde inhalation exposure and the potential for leukemia risk, there is at most only limited suggestive positive evidence, in contrast with the bulk of evidence suggesting no such association. Therefore, a conclusion of causation is not justified scientifically. The scientific landscape into which EPA will release its long-anticipated revised IRIS Toxicological Review of Formaldehyde - Inhalation Assessment is very different from that of the 2010 Draft IRIS Assessment, both in terms of improved methodological approaches and the available epidemiological, toxicological and mechanistic evidence. Given formaldehyde's commercial importance, ubiquity in the environment and endogenous production, accurate determination of whether occupational, residential, or consumer exposure to formaldehyde causes leukemia or any type of human neoplasm is critical.



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Message

From: Thayer, Kris [thayer.kris@epa.gov]

Sent: 9/22/2017 3:19:36 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]

CC: Lavoie, Emma [Lavoie.Emma@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]; Ross, Mary

[Ross.Mary@epa.gov]; Bussard, David [Bussard.David@epa.gov]

Subject: Re: formaldehyde meeting UNC Oct

That may happen....

Sent from my iPhone

On Sep 22, 2017, at 11:17 AM, Bahadori, Tina < Bahadori, Tina@epa.gov> wrote:

Ex. 6 - Personal Privacy

From: Thayer, Kris

Sent: Friday, September 22, 2017 11:14 AM **To:** Lavoie, Emma < Lavoie. Emma@epa.gov>

Cc: Bahadori, Tina < Bahadori, Tina@epa.gov>; Jones, Samantha < Jones. Samantha@epa.gov>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>

Subject: Re: formaldehyde meeting UNC Oct

Yes - I'm attending

Glad Iris will join

Sent from my iPhone

On Sep 22, 2017, at 11:13 AM, Lavoie, Emma <Lavoie. Emma@epa.gov> wrote:

Are we aware of a formaldehyde cancer meeting organized by Mundt at UNC in Oct? Iris Camacho is likely to attend due to invite to Nancy B that filtered to her.

-Emma			

Emma T. Lavoie, PhD
Assistant Center Director for Scientific Support
National Center for Environmental Assessment
US Environmental Protection Agency

Tel: 703-347-0328



From: Kraft, Andrew [Kraft.Andrew@epa.gov]

Sent: 9/26/2017 8:13:25 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Bussard, David

[Bussard.David@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]

CC: Soto, Vicki [Soto.Vicki@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Ramasamy, Santhini

[Ramasamy.Santhini@epa.gov]; Shams, Dahnish [Shams.Dahnish@epa.gov]; Jones, Samantha

[Jones.Samantha@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]

Subject: RE: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 3:53 PM

To: Thayer, Kris <thayer.kris@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Kraft, Andrew

<Kraft.Andrew@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>

Cc: Soto, Vicki <Soto.Vicki@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha

<Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

Т.

From: Thayer, Kris

Sent: Tuesday, September 26, 2017 3:36 PM

To: Bussard, David < Bussard.David@epa.gov >; Bahadori, Tina < Bahadori.Tina@epa.gov >; Kraft, Andrew

<<u>Kraft.Andrew@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>

Cc: Soto, Vicki <Soto. Vicki@epa.gov>; Glenn, Barbara <Glenn. Barbara@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

From: Bussard, David

Sent: Tuesday, September 26, 2017 12:31 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>

Cc: Soto, Vicki <Soto.Vicki@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde



Ex. 5 - Deliberative Process

David

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:16 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov >; Bussard, David < Bussard. David@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Lavoie, Emma < Lavoie. Emma@epa.gov >

Cc: Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

Ex. 5 - Deliberative Process

From: Kraft, Andrew

Sent: Tuesday, September 26, 2017 12:02 PM

To: Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Bussard, David <<u>Bussard, David@epa.gov</u>>; Thayer, Kris <thayer, kris@epa.gov>; Lavoie, Emma <Lavoie, Emma@epa.gov>

Cc: Soto, Vicki < Soto. Vicki@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Ramasamy, Santhini@epa.gov >; Shams, Dahnish < Shams. Dahnish@epa.gov >; Jones, Samantha@epa.gov >; D'Amico, Louis < DAmico.Louis@epa.gov >; Ross, Mary < Ross. Mary@epa.gov >

Subject: RE: Next Steps on Formaldehyde

So, no briefing for OAR next week?

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:02 PM

To: Bussard, David <<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Lavoie, Emma Lavoie.Emma@epa.gov>

Cc: Soto, Vicki <<u>Soto, Vicki@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>QAmico, Louis@epa.gov</u>>; Ross, Mary <<u>Ross, Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde



So jumping back in now – I agree that OPP and OAR are key clients, but OPPT might be as well. So, maybe we do this:

- during the October call we let folks know that this assessment is coming, and that we are likely to transmit documents mid-November;
- that there will be a global briefing during the November Monthly EPA-wide IRIS Call
- and if after hearing that briefing, programs/regions would like additional targeted briefings for their senior management, we are glad to accommodate.

Does this sound OK??

T.

From: Bussard, David

Sent: Tuesday, September 26, 2017 11:42 AM

To: Thayer, Kris <thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>

Cc: Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha

<Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Yes to all this.

If we wanted to pre-brief two offices, my priorities would be OAR and OPP. I don't see how this is a major issue for OW.

David

From: Thayer, Kris

Sent: Tuesday, September 26, 2017 11:39 AM **To:** Lavoie, Emma < <u>Lavoie</u>, Emma@epa.gov>

Cc: Soto, Vicki < Soto. Vicki@epa.gov>; Bahadori, Tina < Bahadori. Tina@epa.gov>; Kraft, Andrew

< Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Bussard, David

"Bussard.David@epa.gov">
"Ramasamy, Santhini Ramasamy, Santhini@epa.gov
"Shams, Dahnish"

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: Re: Next Steps on Formaldehyde

Use of the nov EPA-wide call is a great idea!

Sent from my iPhone

On Sep 26, 2017, at 9:05 AM, Lavoie, Emma < Lavoie. Emma@epa.gov > wrote:

That's all good to hear.

I very much like the idea of using the Nov EPA wide meeting for an overview of the FA assessment.

Have a briefing with OAR first will get us some initial reactions to guide how we present the material to the broader Agency. OW is also interested. Possibly briefing them separately will be helpful. We want positive supportive voices when we present to a big group.



-Emma

Emma T. Lavoie, PhD Tel: 703-347-0328

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 8:27 AM

To: Kraft, Andrew < Kraft, Andrew@epa.gov; Glenn, Barbara < Glenn, Barbara Glenn, Barbara@epa.gov; Lavoie, Emma Lavoie, Emma Lavoie, Emma@epa.gov; Lavoie, Emma@epa.gov

Cc: Ramasamy, Santhini <Ramasamy, Santhini@epa.gov>; Soto, Vicki <Soto.Vicki@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: FW: Next Steps on Formaldehyde

Hi Everyone,

As I said during the IOAA briefing yesterday and note below to Richard, we will plan to move forward with Agency review of the FA assessment. The OAR briefing has been scheduled for 2 PM Tuesday 10/3 – so that will get the ball rolling, right? I suggest we also schedule a broader agency webinar/briefing for later in October/early November. Maybe we can use the November 9^{th} monthly EPA-wide meeting?

Just so we are all on the same page, Andrew and Barbara, can you tell me again when the documents will be ready for transmittal – the overview, the main body of assessment, and appendices. I think we said end of October for the first two? What about the appendices? Once we put this information out there, I would like us to be able to adhere to it. So, can you please confirm?

Other thoughts?

T.

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>

Cc: Kavlock, Robert < Kavlock, Robert@epa.gov>; Rodan, Bruce < rodan.bruce@epa.gov>;

 $Orme-Zavaleta, Jennifer < \underline{Orme-Zavaleta}. \underline{Jennifer@epa.gov}; \ Gwinn, \ Maureen$

<gwinn.maureen@epa.gov>; Sjogren, Mya <Sjogren.Mya@epa.gov>; Kuhn, Kevin

<<u>Kuhn.Kevin@epa.gov</u>>; Fegley, Robert <<u>Fegley.Robert@epa.gov</u>>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<<u>DAmico.Louis@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Bussard, David

<<u>Bussard.David@epa.gov</u>>

Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday - I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to



EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices – Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

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Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)



From: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

**Sent**: 9/26/2017 12:37:14 PM

**To**: Bahadori, Tina [Bahadori.Tina@epa.gov]

Subject: RE: Next Steps on Formaldehyde

Could you share w me a copy of the presentation? thanks

Jennifer Orme-Zavaleta, PhD Director, National Exposure Research Laboratory USEPA Office of Research and Development 109 TW Alexander Dr MC 305-01 RTP, NC 27711

Ex. 6 - Personal Privacy

orme-zavaleta.jennifer@epa.gov

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>

**Cc:** Kavlock, Robert <Kavlock.Robert@epa.gov>; Rodan, Bruce <rodan.bruce@epa.gov>; Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Gwinn, Maureen <gwinn.maureen@epa.gov>; Sjogren, Mya <Sjogren.Mya@epa.gov>; Kuhn, Kevin <Kuhn.Kevin@epa.gov>; Fegley, Robert <Fegley.Robert@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>; Bussard, David <Bussard.David@epa.gov>

Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday – I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices – Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile: [Ex. 6 - Personal Privacy ] Email: Bahadori. Tina@epa.gov



Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov] From:

Sent: 1/3/2018 12:57:12 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]

CC: Yamada, Richard (Yujiro) [yamada.richard@epa.gov] Subject: RE: Next Steps on Formaldehyde IRIS Assessment

Thanks you Tina. Richard and I spoke yesterday on this **Ex. 5 - Deliberative Process** 

Jennifer Orme-Zavaleta, PhD Principal Deputy Assistant Administrator for Science USEPA Office of Research and Development

RTP: Ex. 6 - Personal Privacy (Cell)

orme-zavaleta.jennifer@epa.gov

From: Bahadori, Tina

Sent: Tuesday, January 02, 2018 4:17 PM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov> Cc: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>

Subject: RE: Next Steps on Formaldehyde IRIS Assessment

Dear Jennifer and Richard.

I hope you had a wonderful holiday. I wanted to follow up and see what the timeline for next steps might be for formaldehyde. As you know we have not yet begun Agency briefings or reviews and would like to do so as soon as possible.

Thanks, Tina

From: Bahadori, Tina

Sent: Wednesday, December 20, 2017 8:39 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Cc: Yamada, Richard (Yujiro) < yamada.richard@epa.gov> Subject: RE: Next Steps on Formaldehyde IRIS Assessment

Perfect, thank you. Let me know what I can do – ANYTHING ☺ -- to be helpful.

Tina

From: Orme-Zavaleta, Jennifer

Sent: Wednesday, December 20, 2017 8:19 AM To: Bahadori, Tina < Bahadori, Tina@epa.gov>

Cc: Yamada, Richard (Yujiro) < yamada.richard@epa.gov> Subject: RE: Next Steps on Formaldehyde IRIS Assessment

Thanks Tina, Ex. 5 - Deliberative Process

Jennifer Orme-Zavaleta, PhD Principal Deputy Assistant Administrator for Science



#### **USEPA Office of Research and Development**

DC RTF Ex. 6 - Personal Privacy 919

orme-zavaleta.jennifer@epa.gov

From: Bahadori, Tina

Sent: Wednesday, December 20, 2017 7:55 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta.Jennifer@epa.gov>; Yamada, Richard (Yujiro) < yamada.richard@epa.gov>

Cc: Ross, Mary <Ross.Mary@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<<u>DAmico.Louis@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Bussard, David

<Bussard.David@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Kraft, Andrew

<<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Rodan, Bruce <<u>rodan.bruce@epa.gov</u>>; Christian,

Megan < Christian. Megan@epa.gov>; Kuhn, Kevin < Kuhn. Kevin@epa.gov>; Fleming, Megan < Fleming. Megan@epa.gov>;

Blackburn, Elizabeth < <u>Blackburn</u>. Elizabeth@epa.gov>

Subject: Next Steps on Formaldehyde IRIS Assessment

Good Morning Jennifer and Richard,

I wanted to follow up on the path forward for formaldehyde.

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

# Ex. 5 - Deliberative Process

## Ex. 5 - Deliberative Process

# Ex. 5 - Deliberative Process

We look forward to hearing back from you.



#### Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)
RRB Room 71210; Telephone: 202-564-7903; Mobile Ex. 6 - Personal Privacy

From: Bahadori, Tina

Sent: Thursday, December 7, 2017 8:16 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>; Yamada, Richard (Yujiro) < yamada.richard@epa.gov>

Subject: formaldehyde

Good morning Jennifer and Richard,

Just checking to see if you have an update on path forward for formaldehyde? We would like to at least schedule the 'oral' Agency briefing. It is hard to get on calendars.

Thanks,

Tina



From: Fleming, Megan [Fleming.Megan@epa.gov]

**Sent**: 11/2/2017 3:55:03 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]
Subject: RE: Formaldehyde Science Discussion

Mya is sending a phone line out shortly... \$

Ex. 6 - Personal Privacy

20 6 - 20 20 20 - 20 20 5

Megan Fleming Immediate Office of the Assistant Administrator U.S. EPA Office of Research and Development 1200 Pennsylvania Avenue, N.W. Washington, D.C. 20460 (202)-564-6604

From: Bahadori, Tina

**Sent:** Thursday, November 02, 2017 11:49 AM **To:** Fleming, Megan <Fleming.Megan@epa.gov> **Subject:** RE: Formaldehyde Science Discussion

Megan

Ex. 6 - Personal Privacy | Can you open a phone line for me to call in?

Tina

----Original Appointment----

From: Fleming, Megan On Behalf Of Rodan, Bruce Sent: Thursday, November 2, 2017 11:47 AM

To: Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming, Megan

**Subject:** Formaldehyde Science Discussion

When: Thursday, November 2, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: RRB 41213/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

- Barbara Glenn
- Andrew Kraft
- Tom Bateson
- Kris Thayer

At first glance Tuesday 10/31/17 at noon looks good © on everyone's calendar. Hopefully we can snag that soon!!

Thanks,

Tina



From: Bateson, Thomas [Bateson.Thomas@epa.gov]

**Sent**: 10/25/2017 4:38:43 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew

[Kraft.Andrew@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

CC: Ross, Mary [Ross.Mary@epa.gov]
Subject: RE: Formaldehyde Science Discussion

I will go over to RRB.

Tom

From: Bahadori, Tina

Sent: Wednesday, October 25, 2017 11:50 AM

To: Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Bateson, Thomas

<Bateson.Thomas@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Ross, Mary < Ross. Mary@epa.gov>

Subject: RE: Formaldehyde Science Discussion

This meeting is intended as a focused science discussion just between the four of you with Bruce. I won't participate – neither will David. Should I assume that you will go do the Reagan Building, or do we need video to PYS?

----Original Appointment----

From: Rodan, Bruce

Sent: Wednesday, October 25, 2017 8:55 AM

To: Rodan, Bruce; Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming,

Megan

Subject: Formaldehyde Science Discussion

When: Thursday, November 2, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41226 RRB/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

- Barbara Glenn
- Andrew Kraft
- Tom Bateson
- Kris Thayer

At first glance Tuesday 10/31/17 at noon looks good © on everyone's calendar. Hopefully we can snag that soon!!

Thanks,

Tina



From: Glenn, Barbara [Glenn.Barbara@epa.gov]

**Sent**: 10/25/2017 4:08:49 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Bateson, Thomas

[Bateson.Thomas@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

CC: Ross, Mary [Ross.Mary@epa.gov]
Subject: RE: Formaldehyde Science Discussion

I'll be going over there also.

From: Kraft, Andrew

Sent: Wednesday, October 25, 2017 11:53 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Bateson, Thomas

<Bateson.Thomas@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Ross, Mary < Ross. Mary@epa.gov>

Subject: Re: Formaldehyde Science Discussion

I can head over to the Reagan building.

From: Bahadori, Tina

Sent: Wednesday, October 25, 2017 11:49 AM

To: Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris

Cc: Ross, Mary

Subject: RE: Formaldehyde Science Discussion

This meeting is intended as a focused science discussion just between the four of you with Bruce. I won't participate – neither will David. Should I assume that you will go do the Reagan Building, or do we need video to PYS?

----Original Appointment----

From: Rodan, Bruce

Sent: Wednesday, October 25, 2017 8:55 AM

To: Rodan, Bruce; Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming,

Megan

**Subject:** Formaldehyde Science Discussion

When: Thursday, November 2, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41226 RRB/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

Barbara Glenn



| Andrew Kraft                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------|
| Tom Bateson                                                                                                     |
| Kris Thayer                                                                                                     |
|                                                                                                                 |
| At first glance Tuesday 10/31/17 at noon looks good © on everyone's calendar. Hopefully we can snag that soon!! |
|                                                                                                                 |
| Thanks,                                                                                                         |
| Tina                                                                                                            |
|                                                                                                                 |



From: Bussard, David [Bussard.David@epa.gov]

**Sent**: 9/28/2017 7:55:43 PM

To: Thayer, Kris [thayer.kris@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]

**Subject**: RE: Next Steps on Formaldehyde

### Ex. 5 - Deliberative Process

#### David

From: Thayer, Kris

Sent: Thursday, September 28, 2017 3:30 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov> Cc: Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Soto, Vicki <Soto.Vicki@epa.gov>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

No concerns from me

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 11:31 AM

**To:** Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>> **Cc:** Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

**Subject:** RE: Next Steps on Formaldehyde

### Ex. 5 - Deliberative Process

Τ.

From: Glenn, Barbara

Sent: Thursday, September 28, 2017 11:24 AM

To: Bahadori, Tina <a href="mailto:Kraft">8ahadori.Tina@epa.gov</a>; Kraft, Andrew <a href="mailto:Kraft">Kraft</a>, Andrew <a href="mailto:Kraft">Kraft</a>, Andrew <a href="mailto:Kraft</a>, Andrew <a href="ma

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hi Tina,

# Ex. 5 - Deliberative Process



From: Bahadori, Tina

Sent: Thursday, September 28, 2017 11:10 AM

**To:** Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov">Kraft, Andrew@epa.gov</a>; Glenn, Barbara < <a href="mailto:Glenn.Barbara@epa.gov">Glenn, Barbara@epa.gov</a>; Bussard, David@epa.gov</a>; Bussard, David@epa.gov</a>; Lavoie, Emma < <a href="mailto:Lavoie.Emma@epa.gov">Lavoie.Emma@epa.gov</a></a>; Cc: Ramasamy, Santhini < <a href="mailto:Ramasamy.Santhini@epa.gov">Ramasamy.Santhini@epa.gov</a>; Soto, Vicki < <a href="mailto:Soto.Vicki@epa.gov">Soto.Vicki@epa.gov</a>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Thanks Andrew. So, with this timeline, can we punctuate the rest of the timeline?

### Ex. 5 - Deliberative Process

Tina

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 10:35 AM

To: Bahadori, Tina <a href="mailto:Ramasamy"><u>Ramasamy Santhini@epa.gov</u></a>; Glenn, Barbara <a href="mailto:Glenn.Barbara@epa.gov">Glenn.Barbara@epa.gov</a>; Bussard, David@epa.gov</a>; Bussard, David@epa.gov</a>; Bussard, David@epa.gov</a>; Lavoie, Emma <a href="mailto:Lavoie.Emma@epa.gov">Lavoie, Emma@epa.gov</a>)</a>; Cc: Ramasamy, Santhini <a href="mailto:Ramasamy.Santhini@epa.gov">Ramasamy.Santhini@epa.gov</a>); Soto, Vicki <a href="mailto:Lavoie.Emma@epa.gov">Soto.Vicki@epa.gov</a>); Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

Hi Tina,

I'm not sure Barbara and I followed up with you regarding the tech editing and timeline for Interagency review. We think the goal of early January for Interagency is probably unrealistic (please see below):

### Ex. 5 - Deliberative Process

-Barbara and Andrew



From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:05 PM

To: Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Lavoie, Emma@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki < Soto. Vicki@epa.gov>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

# Ex. 5 - Deliberative Process

Τ.

From: Glenn, Barbara

Sent: Tuesday, September 26, 2017 9:03 AM

To: Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft, Andrew@epa.gov</u>>; Bussard, David <<u>Bussard, David@epa.gov</u>>; Thayer, Kris <<u>thayer, kris@epa.gov</u>>; Lavoie, Emma <<u>Lavoie, Emma@epa.gov</u>> Cc: Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto, Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams, Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones, Samantha@epa.gov</u>>; D'Amico, Louis <DAmico, Louis@epa.gov>; Ross, Mary <Ross, Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hello Tina,

### Ex. 5 - Deliberative Process

Note that these documents will not have been tech edited, although the HERO citations will be inserted. Also the 2017 literature search with sorting and documentation will not be incorporated.

Thanks, Andrew and Barbara

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 8:27 AM

**To:** Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Bussard, David < Bussard. David@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Lavoie, Emma < Lavoie. Emma@epa.gov > Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >; Soto, Vicki < Soto. Vicki@epa.gov >; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: FW: Next Steps on Formaldehyde

Hi Everyone,

As I said during the IOAA briefing yesterday and note below to Richard, we will plan to move forward with Agency review of the FA assessment. The OAR briefing has been scheduled for 2 PM Tuesday 10/3 – so that will get the ball rolling, right? I suggest we also schedule a broader agency webinar/briefing for later in October/early November. Maybe we can use the November 9<sup>th</sup> monthly EPA-wide meeting?



Just so we are all on the same page, Andrew and Barbara, can you tell me again when the documents will be ready for transmittal – the overview, the main body of assessment, and appendices. I think we said end of October for the first two? What about the appendices? Once we put this information out there, I would like us to be able to adhere to it. So, can you please confirm?

Other thoughts?

Τ.

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) < yamada.richard@epa.gov>

Cc: Kavlock, Robert <Kavlock.Robert@epa.gov>; Rodan, Bruce <rodan.bruce@epa.gov>; Orme-Zavaleta, Jennifer

<Orme-Zavaleta.Jennifer@epa.gov>; Gwinn, Maureen <gwinn.maureen@epa.gov>; Sjogren, Mya

<<u>Sjogren.Mya@epa.gov</u>>; Kuhn, Kevin <<u>Kuhn.Kevin@epa.gov</u>>; Fegley, Robert <<u>Fegley.Robert@epa.gov</u>>; Ross,

Mary <Ross.Mary@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<<u>DAmico.Louis@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>

Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday — I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices — Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile Ex.6-Personal Privacy Email: Bahadori.Tina@epa.gov



From: Bussard, David [Bussard.David@epa.gov]

**Sent**: 2/7/2018 3:59:58 PM

**To**: Bahadori, Tina [Bahadori.Tina@epa.gov]

**Subject**: RE: Formaldehyde Fact Sheet

Good. Many thanks.

From: Bahadori, Tina

Sent: Wednesday, February 07, 2018 10:53 AM

To: Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>

Subject: RE: Formaldehyde Fact Sheet

See if my **responses** help.

From: Bussard, David

Sent: Wednesday, February 7, 2018 9:59 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>

Subject: RE: Formaldehyde Fact Sheet

Kris and Tina,

Thanks. Let me check a few things. Questions in red. Possible edits in blue.

## Ex. 5 - Deliberative Process



## Ex. 5 - Deliberative Process

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From: Bahadori, Tina

Sent: Wednesday, February 07, 2018 9:06 AM

To: Thayer, Kris < thayer.kris@epa.gov>; Bussard, David < Bussard.David@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>

Subject: RE: Formaldehyde Fact Sheet

### Ex. 5 - Deliberative Process

From: Thayer, Kris

**Sent:** Tuesday, February 6, 2018 8:03 PM **To:** Bussard, David <a href="mailto:Bussard.David@epa.gov">Bussard.David@epa.gov</a>

Cc: Bahadori, Tina <Bahadori. Tina@epa.gov>; Ramasamy, Santhini <Ramasamy. Santhini@epa.gov>

Subject: RE: Formaldehyde Fact Sheet

### Ex. 5 - Deliberative Process

From: Bussard, David

**Sent:** Tuesday, February 6, 2018 8:00 PM **To:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>>

Cc: Bahadori, Tina <Bahadori, Tina@epa.gov>; Ramasamy, Santhini <Ramasamy, Santhini@epa.gov>

Subject: Re: Formaldehyde Fact Sheet

We could add NAS review of NTP finding.

### Ex. 5 - Deliberative Process

David Bussard

On Feb 6, 2018, at 7:58 PM, Thayer, Kris <thayer.kris@epa.gov> wrote:



### Ex. 5 - Deliberative Process

From: Bussard, David

Sent: Tuesday, February 6, 2018 2:59 PM

To: Bahadori, Tina <Bahadori. Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>

Subject: Formaldehyde Fact Sheet

Tina and Kris,

We will fill in some blanks (some are highlighted) and do QA.

But, can you look to see if this it at the level you want.

### Ex. 5 - Deliberative Process

David A. Bussard

Director, Washington Division, National Center for Environmental Assessment (NCEA) Office of Research and Development (ORD), USEPA

Tel: 202-564-4113; office RRB Room 71254



From: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

**Sent**: 12/5/2017 12:57:43 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Yamada, Richard (Yujiro) [yamada.richard@epa.gov]
CC: Christian, Megan [Christian.Megan@epa.gov]; Kuhn, Kevin [Kuhn.Kevin@epa.gov]; Thayer, Kris

[thayer.kris@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn,

Barbara [Glenn.Barbara@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Ramasamy, Santhini

[Ramasamy.Santhini@epa.gov]

**Subject**: RE: Formaldehyde materials you requested

Thanks! And thanks again for the briefing. Very helpful

Jennifer Orme-Zavaleta, PhD
Principal Deputy Assistant Administrator for Science
USEPA Office of Research and Development

DC: Ex. 6 - Personal Privacy
RTP
Ex. 6 - Personal Privacy (Cell)

orme-zavaleta.jennifer@epa.gov

From: Bahadori, Tina

Sent: Monday, December 04, 2017 6:43 PM

To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Yamada, Richard (Yujiro) <yamada.richard@epa.gov>

Cc: Christian, Megan < Christian. Megan@epa.gov>; Kuhn, Kevin < Kuhn. Kevin@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn,

Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>

Subject: Formaldehyde materials you requested

Dear Jennifer and Richard,

Attached are a) the slides from today's briefing, and b) the agenda from the IRIS Formaldehyde workshop in 2014. The agenda provides a good outlook on the sessions, discussion questions, and who led them.

### Ex. 5 - Deliberative Process

Please let us know if you need anything else.

Tina

From: Glenn, Barbara

**Sent:** Monday, December 4, 2017 4:52 PM **To:** Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>

Cc: Bussard, David <<u>Bussard.David@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Thayer, Kris

<thayer.kris@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Subject: Material requested by IOAA

Hi Tina,

Attached are the slides from today's presentation. Jennifer expressed an interest in the first 10 slides, but we thought if she had all of the slides, then she could use them as she wished. Do you think she wanted them in a different format?



Also attached is the agenda from the 2014 workshop on formaldehyde organized by NCEA. It contained the chairs, speakers, discussants and discussion questions for each session.

Next week we will be able to send you some bullets pertaining to some comments from stakeholders and how the assessment discusses the issues.

Regards, Barbara and Andrew



From: D'Amico, Louis [DAmico.Louis@epa.gov]

**Sent**: 12/19/2017 7:43:41 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]

CC: Jones, Samantha [Jones.Samantha@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Bussard, David

[Bussard.David@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Ross, Mary [Ross.Mary@epa.gov];

Glenn, Barbara [Glenn.Barbara@epa.gov]

**Subject**: RE: Your input -- formaldehyde

Nothing from me that hasn't already been pointed out.

-Lou

(NOTE NEW CONTACT

INFORMATION)

Louis D'Amico, Ph.D.

Assistant Center Director, Communications and Regulatory Support - National Center for Environmental Assessment Associate Director for Policy and Communications - Human Health Risk Assessment National Research Program U.S. EPA Office of Research and Development

damico.louis@epa.gov

O: (202) 564-4605 M: Ex. 6 - Personal Privacy

From: Kraft, Andrew

**Sent:** Tuesday, December 19, 2017 10:18 AM **To:** Bahadori, Tina <Bahadori.Tina@epa.gov>

Cc: Jones, Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>; Lavoie, Emma

<Lavoie.Emma@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>

Subject: RE: Your input -- formaldehyde

### Ex. 5 - Deliberative Process

-Andrew

From: Bahadori, Tina

**Sent:** Tuesday, December 19, 2017 9:48 AM **To:** Kraft, Andrew < Kraft. Andrew @epa.gov>

Cc: Jones, Samantha < Jones, Samantha@epa.gov>; D'Amico, Louis < DAmico, Louis@epa.gov>; Lavoie, Emma

<Lavoie.Emma@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini

<<u>Ramasamy.Santhini@epa.gov></u>; Ross, Mary <<u>Ross,Mary@epa.gov></u>; Glenn, Barbara <<u>Glenn,Barbara@epa.gov></u>

Subject: RE: Your input -- formaldehyde

### Ex. 5 - Deliberative Process

Τ.

From: Kraft, Andrew

**Sent:** Tuesday, December 19, 2017 8:51 AM **To:** Bahadori, Tina@epa.gov>

Cc: Jones, Samantha < Jones, Samantha@epa.gov>; D'Amico, Louis < DAmico, Louis@epa.gov>; Lavoie, Emma



<<u>Lavoie.Emma@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>> Subject: RE: Your input -- formaldehyde

Hi Tina,

I also think it is a great letter. Just a few minor editing suggestions from me (in blue below).

### Ex. 5 - Deliberative Process

Of course, I am assuming the traditional steps, but September transmittal seems questionable to me.

Thank you, Andrew

From: Ross, Mary

Sent: Tuesday, December 19, 2017 8:31 AM To: Glenn, Barbara < Glenn. Barbara@epa.gov>

Cc: Bahadori, Tina <Bahadori. Tina@epa.gov>; Jones, Samantha <Jones. Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bussard, David <Bussard.David@epa.gov>;

Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Kraft, Andrew < Kraft. Andrew@epa.gov>

Subject: Re: Your input -- formaldehyde

Excellent!

Sent from my iPhone

On Dec 19, 2017, at 8:21 AM, Glenn, Barbara < Glenn.Barbara@epa.gov > wrote:

From: Bahadori, Tina

Sent: Tuesday, December 19, 2017 7:54 AM

To: Ross, Mary <Ross.Mary@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Kraft, Andrew

<<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>

Subject: Your input -- formaldehyde

I like it. I just suggest some little edits (in red in 2<sup>nd</sup> and 4<sup>th</sup> paragraphs). Thank you for sending it.

-Barbara

This is what I am thinking of sending the IOAA today – let me know what you think and feel free to suggest any changes:

### Ex. 5 - Deliberative Process



We look forward to hearing back from you.

Tina

From: Bahadori, Tina

Sent: Thursday, December 7, 2017 8:16 AM

To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Yamada, Richard (Yujiro)

<yamada.richard@epa.gov>
Subject: formaldehyde

Good morning Jennifer and Richard,

Just checking to see if you have an update on path forward for formaldehyde? We would like to at least schedule the 'oral' Agency briefing. It is hard to get on calendars.



Thanks, Tina



From: Bahadori, Tina [Bahadori.Tina@epa.gov]

**Sent**: 1/23/2018 7:24:15 AM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]

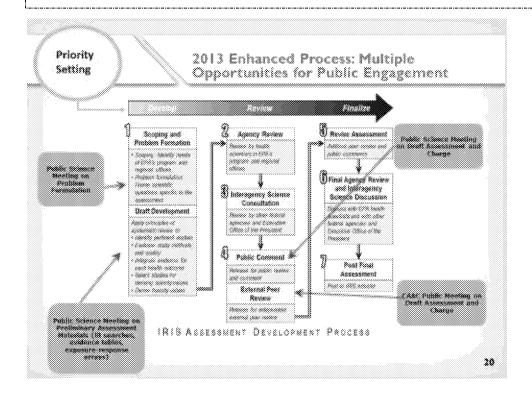
**Subject**: tracking the evolution of formaldehyde briefings

Attachments: FW: Follow-up; RE: Formaldehyde Science Invited Expert Workshop; FW: Submission of Letter on Behalf of the ACC

Formaldehyde Panel; Letter Submitted on Behalf of the ACC Formaldehyde Panel; Next Steps on Formaldehyde IRIS

Assessment

### Ex. 5 - Deliberative Process





From: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

**Sent**: 12/4/2017 1:49:33 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

Subject: FW: Follow-up

Attachments: Mundt et al 2017 - Six Year aftr NRC Review.pdf

To start your week...

Jennifer Orme-Zavaleta, PhD
Principal Deputy Assistant Administrator for Science
USEPA Office of Research and Development

RTF. Ex. 6 - Personal Privacy

Ex. 6 - Personal Privacy

orme-zavaleta.jennifer@epa.gov

From: White, Kimberly [mailto:Kimberly\_White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21<sup>st</sup> letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22<sup>nd</sup> to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

+++++

<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

<u>Mundt KA<sup>1</sup></u>, <u>Gentry PR<sup>2</sup></u>, <u>Dell LD<sup>2</sup></u>, <u>Rodricks JV<sup>2</sup></u>, <u>Boffetta P<sup>3</sup></u>. <u>Author information</u>

Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify



and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

#### **KEYWORDS:**

| chideimotogy, i | Evidence integration | , nazaru evaluation, <i>i</i> | mechanistic studies, | Regulatory science, | Toxicology    |
|-----------------|----------------------|-------------------------------|----------------------|---------------------|---------------|
|                 |                      |                               |                      |                     |               |
| ++++++++++      | ++++++++++++++       | +++++++++++                   | +++++++++++++++      | ++++++++++          | +++++++++++++ |
| ++              |                      |                               |                      |                     |               |

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly\_White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com



### **Accepted Manuscript**

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity

Kenneth A. Mundt, P. Robinan Gentry, Linda D. Dell, Joseph V. Rodricks, Paolo Boffetta

PII: S0273-2300(17)30363-X

DOI: 10.1016/j.yrtph.2017.11.006

Reference: YRTPH 3987

To appear in: Regulatory Toxicology and Pharmacology

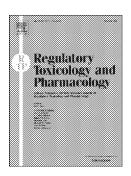
Received Date: 7 April 2017

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Please cite this article as: Mundt, K.A., Gentry, P.R., Dell, L.D., Rodricks, J.V., Boffetta, P., Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity, *Regulatory Toxicology and Pharmacology* (2017), doi: 10.1016/j.yrtph.2017.11.006.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.





| 1<br>2 | Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity |
|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3      |                                                                                                                                                                            |
| 4      | Mundt, Kenneth A. <sup>1</sup>                                                                                                                                             |
| 5      | Gentry, P. Robinan <sup>1</sup>                                                                                                                                            |
| 6      | Dell, Linda D. <sup>1</sup>                                                                                                                                                |
| 7      | Rodricks, Joseph V. <sup>1</sup>                                                                                                                                           |
| 8      | Boffetta, Paolo <sup>2</sup>                                                                                                                                               |
| 9      |                                                                                                                                                                            |
| 10     | <sup>1</sup> Environment and Health, Ramboll Environ US Corporation, Amherst MA                                                                                            |
| 11     | <sup>2</sup> Icahn School of Medicine at Mount Sinai, New York, New York, USA                                                                                              |
| 12     |                                                                                                                                                                            |
| 13     | Address correspondence to:                                                                                                                                                 |
| 14     | Dr. Kenneth A. Mundt                                                                                                                                                       |
| 15     | kmundt@ramboll.com                                                                                                                                                         |
| 16     | +1.413.835.4360                                                                                                                                                            |
| 17     |                                                                                                                                                                            |
| 18     | WORD COUNTS:                                                                                                                                                               |
| 19     | Abstract (limit 200): 194                                                                                                                                                  |
| 20     | Text: 12,694                                                                                                                                                               |
| 21     | References:                                                                                                                                                                |
| 22     |                                                                                                                                                                            |
| 23     | Keywords (limit 10): 10                                                                                                                                                    |
| 24     | Abbreviations                                                                                                                                                              |
| 25     |                                                                                                                                                                            |
| 26     |                                                                                                                                                                            |



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- 2 Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde
- 3 causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS
- 4 Toxicological Review of Formaldehyde, also concluding that formaldehyde causes leukemia. Peer review
- 5 of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal
- determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered
- 7 recommendations for improving the IRIS review and identified several important research gaps. Over
  - the six years since the NRC peer review, significant new science has been published. We identify and
- 9 summarize key NRC recommendations and map them to this new science, including extended analysis of
- 10 epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using
- 11 a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous
- 12 formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are
- consistently negative, and integration of all available evidence challenges the earlier conclusions that
- 14 formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity
- and endogenous production, accurate hazard classification and risk evaluation of whether exposure to
- 16 formaldehyde from occupational, residential and consumer products causes leukemia are critical.

18

8

- Key Words: Regulatory science, hazard evaluation, evidence integration, epidemiology, toxicology,
- 19 mechanistic studies

20



### 1 1.0 Introduction

| 2  | classification and regulation of number carefulgens is a key component to the protection and               |
|----|------------------------------------------------------------------------------------------------------------|
| 3  | improvement of public health. However, proper regulation of industrial chemicals hinges on both valid      |
| 4  | hazard identification and quantitative risk assessment. Increasingly, hazard identification – at least     |
| 5  | where adequate scientific evidence is available – draws on critically assessing and integrating evidence   |
| 6  | across lines of inquiry including animal and human toxicology (e.g., pharmacokinetic, mechanistic          |
| 7  | studies) and epidemiology. Quantitative risk assessment requires reasonably accurate characterization      |
| 8  | of exposures, which is complicated, especially where historical measures are sparse or do not exist.       |
| 9  | Where adequate evidence from some or all of these is lacking, and where important uncertainties            |
| 10 | remain, policy-driven approaches favoring precaution are warranted. On the other hand, as evidence         |
| 11 | accumulates, more science-focused methods can be employed, reducing uncertainties, leading to              |
| 12 | sounder conclusions. Nevertheless, confident conclusions are sometimes drawn prematurely, as               |
| 13 | discussed in this commentary. Recent evaluations of formaldehyde, coupled with improved critical           |
| 14 | review and evidence integration expectations and new, more focused scientific evaluations, illustrate      |
| 15 | the dynamic nature of scientific inquiry and the need for parallel refinement of hazard characterization,  |
| 16 | and subsequently, stronger risk assessment.                                                                |
|    |                                                                                                            |
| 17 | In this paper, we illustrate the evolution of new scientific evidence on formaldehyde as a potential       |
| 18 | human leukemogen. The impetus for the new science summarized below is derived from the                     |
| 19 | International Agency for Research on Cancer's (IARC) 2009 classification of formaldehyde as a known        |
| 20 | cause of leukemia in Monograph 100F (Baan, et al. 2009; IARC, 2012), the US Environmental Protection       |
| 21 | Agency's (EPA's) similar classification in a Draft IRIS (Integrated Risk Information System) Toxicological |
| 22 | Review of Formaldehyde – Inhalation Assessment (hereafter referred to as the "Draft IRIS Assessment")      |
| 23 | (EPA 2010), and the criticisms and recommendations presented in two National Academy of Science            |
| 24 | (NAS), National Research Council (NRC) expert reviews – one on the Draft IRIS Assessment and one on        |



- the IRIS process itself (EPA 2010; IARC 2012; NRC 2011; NRC 2014a). Various organizations and agencies
- 2 have contributed to or sponsored the new science, including governments and universities, as well as
- 3 industry. In revising and finalizing the Draft IRIS Assessment (EPA 2010), EPA now has the opportunity to
- 4 incorporate the new evidence in addressing many of the issues raised by the NRC reviews.

#### 5 2.0 Formaldehyde Cancer Hazard Evaluation

- 6 The carcinogenicity of formaldehyde has been evaluated by several agencies since the early 1980s,
- 7 including the IARC, the National Toxicology Program (NTP) of the National Institute for Environmental
- 8 Health Sciences (NIEHS), the EPA, and most recently, the Committee for Risk Assessment (RAC) of the
- 9 European Chemicals Agency (ECHA) and the Scientific Committee on Occupational Exposure Limits
- 10 (SCOEL) of the European Commission (table 1). Except for the RAC review (RAC 2012) and the SCOEL
- review (Bolt et al. 2016), which reclassified formaldehyde as a Carcinogen Category 1B (i.e., presumed
- 12 to have carcinogenic potential for humans) and a Category C carcinogen (i.e., genotoxic carcinogen with
- a mode of action based threshold), respectively, these reviews classified formaldehyde as a known
- 14 human carcinogen, primarily based on NPC but also on lymphohematopoietic malignancies (LHM) as a
- group and/or all leukemias as a group, and all myeloid leukemias (ML) as a group (EPA 2010; IARC 2012;
- 16 NTP 2011). Differences between NTP (2012) and EPA draft classifications (final version of the EPA
- 17 review is pending) have been highlighted by Rhomberg (2015a) and differences between the IARC
- 18 (2012) and the RAC (RAC ECHA, 2012) evaluations have been discussed by Marsh et al (2014).
- 19 The reviews by authoritative bodies acknowledged that hazard identification for formaldehyde was not
- 20 straightforward, especially with respect to possible leukemogenicity, in part due to its endogenous
- 21 production and high reactivity. This prompted closer scrutiny regarding the methods used to critically
- 22 evaluate the strength and quality of scientific studies, and ultimately, how best to integrate evidence
- 23 across lines of inquiry such as animal, mechanistic and epidemiological evaluations.



| 1  | IARC first classified formaldehyde as "carcinogenic to humans" (i.e., Group 1) in 2005 (Cogliano, et al.  |
|----|-----------------------------------------------------------------------------------------------------------|
| 2  | 2005; IARC 2006), revising the previous evaluation in 1995 that formaldehyde is "probably carcinogenic    |
| 3  | to humans" (i.e., Group 2A) (Table 1). The 2005 evaluation concluded that formaldehyde causes NPC,        |
| 4  | based primarily on results from animal studies, with additional evidence from "the largest and most       |
| 5  | informative cohort study of industrial workers" (i.e., Hauptmann, et al. 2004, Cogliano et al., 2005).    |
| 6  | Results from animal studies demonstrated that formaldehyde in direct contact with nasal passage           |
| 7  | tissues induced tumors at formaldehyde concentrations > 2 ppm as summarized by Nielsen and Wolkoff        |
| 8  | (2013) and later by Nielsen, et al. (2017). This was considered consistent with formaldehyde's            |
| 9  | demonstrated genotoxicity, and with the "sufficient epidemiological evidence that formaldehyde causes     |
| 10 | nasopharyngeal cancer in humans" (IARC 2006).                                                             |
| 11 | IARC (2012) concluded that formaldehyde also causes leukemia, and in particular ML, although that         |
| 12 | Working Group noted that it was a "small majority" who found the evidence as sufficient. Neither          |
| 13 | Hauptmann, et al. (2003) nor the subsequently updated study (Beane Freeman, et al. 2009) published        |
| 14 | results specifically for acute myeloid leukemia (AML). The Working Group noted a study reporting          |
| 15 | aneuploidy in the blood of exposed workers (Zhang, et al. 2010), recently accepted for publication,       |
| 16 | provided supporting data, with the caveat that the study needed to be replicated (IARC 2012). Indeed,     |
| 17 | proper replication of this study is still needed, because the study protocol was not consistent with      |
| 18 | adequate cell counting standards, including the authors' earlier descriptions of the OctoChrome FISH      |
| 19 | method (Zhang, et al. 2005; Zhang, et al. 2011) and other standards (American Society of Medical          |
| 20 | Genetics, 2006). One particular challenge is that occupational exposure limits in North America, Europe   |
| 21 | and in many countries around the world protect workers from the levels of occupational formaldehyde       |
| 22 | exposures that were studied by Zhang, et al. (2010) in China making replication of the study logistically |



difficult. Proper replication of this study also will require use of methods to successfully distinguish

- 1 between an euploidy arising in vivo from an euploidy that arises during the period of in vitro culture, as
- 2 discussed in section 3.3.3 below.
- 3 Following the IARC review and classification, the National Toxicology Program (NTP) concluded that
- 4 formaldehyde causes nasopharyngeal cancer and myeloid leukemia in the 12<sup>th</sup> Report on Carcinogens
- 5 (NTP 2012) (Table 1). The 12<sup>th</sup> RoC stated "The most informative studies for evaluation of the risk of ML
- 6 are the large cohort studies of industrial workers (the NCI, NIOSH, and British cohorts) and the NCI
- 7 nested case-control study<sup>1</sup> of lymphohematopoietic cancer in embalmers" and specifically that "Three of
- 8 these four studies found elevated risks of myeloid leukemia among individuals with high exposure to
- 9 formaldehyde, as well as positive exposure-response relationships". However, the NTP also noted "In
- 10 the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde
- exposure" and that in the only case-control study examining ML (Blair, et al. 2000) "an excess risk was
- found for chronic (but not acute) myeloid leukemia" (NTP, RoC, 12<sup>th</sup> edition, "Formaldehyde", p.3).

### 2.1 Environmental Protection Agency Integrated Risk Assessment Program (IRIS)

- 14 Formaldehyde had been classified by the EPA as a "probable" human carcinogen (Group 1B) in 1991
- 15 (Table 1). An updated assessment for public review and comment was first released in June 2010, 12
- 16 years after the EPA announced the re-evaluation, and the draft assessment reported that formaldehyde
- 17 causes NPC, nasal and paranasal cancer, lymphohematopoietic cancers, all leukemias, and ML (Table 1).
- The EPA (2010) also derived a draft inhalation unit risk (IUR) value of  $8.1 \times 10^{-2}$  per ppm ( $6.6 \times 10^{-5}$  per
- 19  $\mu g/m^3$ )<sup>2</sup> based on the upper bound on the sum of the risk estimates for NPC, Hodgkin lymphoma, and



<sup>&</sup>lt;sup>1</sup> This study technically is not a "nested case-control study" but rather a pooled reanalysis of death certificate data from several published proportionate mortality ratio (PMR) analyses, using a case-control approach. Thus, it carries the same limitations of death certificate analyses performed outside of a well enumerated cohort, and therefore is not "nested" in any true cohort that could be accurately enumerated.

<sup>&</sup>lt;sup>2</sup> This is 15 times higher than the inhalation unit risk (IUR) derived by EPA for vinyl chloride ( $4.4 \times 10^{-6}$  per  $\mu g/m^3$ ) (EPA 2000, page 50), a chemical for which the evidence clearly supports a causal association between exposure and effects in both animals and humans.

| 1  | leukemia (combined risks) based on part of the results reported in Beane Freeman et al. (2009). For         |
|----|-------------------------------------------------------------------------------------------------------------|
| 2  | rationale, the EPA said the classification "is supported by cohort analyses of embalmers, pathologists      |
| 3  | and anatomists (Hall, et al. 1991; Hayes, et al. 1990; Levine, et al. 1984; Matanoski 1989; Stroup, et al.  |
| 4  | 1986; Walrath, Fraumeni 1983, 1984; Yuan, et al.2007)" despite the observation that " SMR analyses          |
| 5  | of the large industrial cohorts do not indicate a similar association (Beane Freeman, et al. 2009; Coggon,  |
| 6  | et al. 2003; Pinkerton, et al. 2004)" (page 4-180). The EPA also cited three meta-analyses (Bosetti, et al. |
| 7  | 2008; Collins and Lineker 2004; Zhang et al. 2009) that largely included the same studies as providing      |
| 8  | additional evidence. Repeatedly reporting the same results, however, does not constitute independent        |
| 9  | or additional evidence. Similarly, all meta-analyses included earlier versions of the NCI cohort workers    |
| 10 | and embalmers studies and therefore, they, too, are redundant with the meta-analyses.                       |
| 11 | The conclusions in the EPA Draft specific to myeloid leukemia are as follows:                               |
| 12 | "Given the consistency of the positive associations for formaldehyde with myeloid                           |
| 13 | leukemia cancer mortality across five of the six studies (Hauptmann, et al. 2009; Hayes,                    |
| 14 | et al. 1990; Pinkerton, et al. 2004; Stroup, et al. 1986; Walrath and Fraumeni 1984;                        |
| 15 | Walrath and Fraumeni, 1983; but not Beane Freeman, et al. 2009), the statistically                          |
| 16 | significant meta-analysis by Zhang et al. (2009) and the convincing results from                            |
| 17 | Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude                         |
| 18 | that there is a causal association between formaldehyde exposure and mortality from                         |
| 19 | myeloid leukemia." (EPA 2010) (pages 4-184, 4-185)                                                          |
| 20 |                                                                                                             |
| 21 | Again, because of the significant overlap between Hauptmann et al. (2009) and the three PMR studies of      |
| 22 | funeral directors and embalmers (Hayes, et al. 1990; Walrath, Fraumeni 1983, 1984) these overlapping        |

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reports do not constitute independent evidence or consistency across studies. Hauptmann et al. (2009)

has been judged to have severe methodological flaws (Cole et al. 2010a; b); as such, these results are

not convincing. Separately, the Zhang et al. (2009) meta-analysis combined different exposure metrics

(peak, average intensity, cumulative exposure, duration), and thus, the exposure metrics were not

comparable across studies. A more methodologically rigorous approach would be to perform meta-

analyses for similar exposure metrics, that is, a meta-RR for cumulative exposure, meta-RR for average

| 1                                      | exposure, meta-RR for duration of exposure (only one study reported results in relation to peak                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2                                      | exposure, precluding a meta-analysis for peak exposure). As such, the Zhang (2009) meta-analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 3                                      | results are difficult to interpret and methodologically flawed. Finally, combining data in a meta-analyses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 4                                      | does not overcome any systematic biases in the underlying studies (Greenland and Longnecker, 1992).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 5                                      | 2.2 National Academies Peer-Review Process                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 6                                      | The NRC of the NAS, at the request of the EPA, formed an expert Committee to perform the peer-review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 7                                      | of the EPA Draft. Following a series of meetings during the second half of 2010, the NRC issued the final                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 8                                      | report on April 8, 2011 (NRC 2011) as a pre-publication copy. The Committee identified numerous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 9                                      | constructive criticisms and data gaps, and provided recommendations for improving IRIS reviews in                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 10                                     | general (NRC 2011). Though not directly charged to evaluate the EPA Draft conclusions, the peer review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 11                                     | raised important questions regarding the underlying methods giving rise to several conclusions,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 12                                     | including the basic causal conclusions:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 13<br>14<br>15<br>16<br>17<br>18<br>19 | "EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers—"all LHP cancers," "all leukemias," and "myeloid leukemias." The committee does not support the grouping of "all LHP cancers" because it combines many diverse cancers that are not closely related in etiology and cells of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas." (NRC 2011, Summary, page 11) |
| 20                                     | The Committee concluded that EPA's claims that formaldehyde causes leukemia, ML or related                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 21                                     | hematopoietic cancers were not supported in EPA's assessment, appeared to be subjective in nature,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 22                                     | and that no clear scientific framework had been applied by EPA in reaching that conclusion (NRC 2011).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 23                                     | The absence of such a framework was judged by the committee as problematic:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 24                                     | "As with the respiratory tract cancers, the draft IRIS assessment does not provide a clear                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 25                                     | framework for causal determinations. As a result, the conclusions appear to be based on                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 26                                     | a subjective view of the overall data, and the absence of a causal framework for these                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 27                                     | cancers is particularly problematic given the inconsistencies in the epidemiologic data,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 28                                     | the weak animal data, and the lack of mechanistic data. Although EPA provided an                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 29                                     | exhaustive description of the studies and speculated extensively on possible modes of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |



| 1<br>2<br>3<br>4<br>5<br>6<br>7 | action, the causal determinations are not supported by the narrative provided in the draft IRIS assessment. Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to its conclusions." (page 11, NRC 2011) |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 | The NIDC fourthern we find a department of the CDA (2010) are always as the office and always are always as a find a second of the CDA (2010).                                                                                                                                                                                                                                                                                                              |
| 8                               | The NRC further pointed out that that EPA (2010) conclusion that formaldehyde causes ML was based                                                                                                                                                                                                                                                                                                                                                           |
| 9                               | primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action)                                                                                                                                                                                                                                                                                                                                                       |
| 10                              | were not considered beyond studies conducted by Zhang et al. (2009, 2010).                                                                                                                                                                                                                                                                                                                                                                                  |
| 11                              | In the 7th and final chapter of its review, entitled, "A Roadmap for Revision," the NRC provided                                                                                                                                                                                                                                                                                                                                                            |
| 12                              | recommendations in two categories: "Critical Revisions of the Current Draft IRIS Assessment of                                                                                                                                                                                                                                                                                                                                                              |
| 13                              | Formaldehyde," and "Future Assessments and the IRIS Process" (NRC 2011). NRC (2011) specifically                                                                                                                                                                                                                                                                                                                                                            |
| 14                              | identified the systematic review standards adopted by the Institute of Medicine (IOM), as being                                                                                                                                                                                                                                                                                                                                                             |
| 15                              | appropriate for such an analysis (IOM 2011).                                                                                                                                                                                                                                                                                                                                                                                                                |
| 16                              | Following the release of the NRC (2011) peer review, Congress issued House Report No. 112-151, and                                                                                                                                                                                                                                                                                                                                                          |
| 17                              | directed EPA to incorporate recommendations of Chapter 7 of the NRC (2011) report into the IRIS                                                                                                                                                                                                                                                                                                                                                             |
| 18                              | process. In 2014, NRC released an additional report on the IRIS process (NRC 2014a), and emphasized                                                                                                                                                                                                                                                                                                                                                         |
| 19                              | the importance of evidence integration for hazard identification, in which studies of higher quality and                                                                                                                                                                                                                                                                                                                                                    |
| 20                              | low risk of bias are given greater weight in drawing conclusions regarding causality.                                                                                                                                                                                                                                                                                                                                                                       |
| 21                              | As part of their response to the NRC reviews, the EPA convened a state-of-the-science workshop on                                                                                                                                                                                                                                                                                                                                                           |
| 22                              | formaldehyde on April 30 and May 1, 2014 in Arlington, Virginia. This workshop focused on three                                                                                                                                                                                                                                                                                                                                                             |
| 23                              | themes:                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 24<br>25<br>26<br>27<br>28      | <ul> <li>Evidence pertaining to the influence of formaldehyde that is produced endogenously (by the body during normal biological processes) on the toxicity of inhaled formaldehyde, and implications for the health assessment;</li> <li>Mechanistic evidence relevant to formaldehyde inhalation exposure and lymphohematopoietic cancers (leukemia and lymphomas); and</li> </ul>                                                                       |



| 1<br>2<br>3<br>4 | <ul> <li>Epidemiological research examining the potential association between formaldehyde exposure<br/>and lymphohematopoietic cancers (leukemia and lymphomas).</li> <li>(From: <a href="https://www.epa.gov/iris/formaldehyde-workshop">https://www.epa.gov/iris/formaldehyde-workshop</a>)</li> </ul> |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5                | A second workshop was announced at the meeting but never was convened. Since then, House Report                                                                                                                                                                                                           |
| 6                | No. 114-632 (page 57-59) and Senate Report No. 114-281 (page 62) have requested the allocation of                                                                                                                                                                                                         |
| 7                | funds for NRC to peer review the revised IRIS Toxicological Review of Formaldehyde, to ensure that                                                                                                                                                                                                        |
| 8                | recommendations raised by the NRC (2011) were implemented.                                                                                                                                                                                                                                                |
| 10               | 3.0 New studies published since the 2011 NRC Peer Review of the Draft IRIS Assessment                                                                                                                                                                                                                     |
|                  |                                                                                                                                                                                                                                                                                                           |
| 11               | Numerous studies and updated analyses have been published since the 2011 NRC Peer Review of the                                                                                                                                                                                                           |
| 12               | Draft IRIS Assessment, the findings of which, at least in part, fill many of the "data gaps" and address                                                                                                                                                                                                  |
| 13               | several key methodological issues highlighted in the NRC Committee recommendations (2011). Below                                                                                                                                                                                                          |
| 14               | we summarize this new research, organized around the data streams (e.g., epidemiological,                                                                                                                                                                                                                 |
| 15               | toxicological, and mode of action) for evidence integration and quantification of potential leukemia                                                                                                                                                                                                      |
| 16               | risks, specifically responsive to the following NRC recommendations (2011) (page reference provided):                                                                                                                                                                                                     |
|                  |                                                                                                                                                                                                                                                                                                           |
| 17               | $\infty$ Epidemiological Evidence                                                                                                                                                                                                                                                                         |
| 18               | ∞ Discussion of the specific strengths, weaknesses and inconsistencies in several key                                                                                                                                                                                                                     |
| 19<br>20         | studies, as the draft IRIS assessment relies solely on epidemiologic studies to determine causality. $(p.113)$                                                                                                                                                                                            |
| 21               | ∞ Clarification of the basis of its interpretations of the results regarding the various dose                                                                                                                                                                                                             |
| 22               | metrics (peak versus cumulative) and the various LHP cancers. (p.113)                                                                                                                                                                                                                                     |
| 23               | ∞ Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute                                                                                                                                                                                                              |
| 24               | myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas).                                                                                                                                                                                                                       |
| 25               | (p. 113)                                                                                                                                                                                                                                                                                                  |
| 26               |                                                                                                                                                                                                                                                                                                           |
| 27               | ∞ Toxicological Evidence                                                                                                                                                                                                                                                                                  |
| 28               | $\infty$ Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's                                                                                                                                                                                                                  |
| 29               | unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle                                                                                                                                                                                                                    |
| 30               | Columbus Laboratories 1981), although intriguing, provides the only positive findings                                                                                                                                                                                                                     |
| 31               | and thus does not contribute to the weight of evidence of causality. $(p.110)$                                                                                                                                                                                                                            |
| 32               |                                                                                                                                                                                                                                                                                                           |



| 1  | $\infty$     | Mo       | ode of Action Evidence                                                                        |
|----|--------------|----------|-----------------------------------------------------------------------------------------------|
| 2  |              | $\infty$ | Improving the understanding of when exogenous formaldehyde exposure appreciably               |
| 3  |              |          | alters normal endogenous formaldehyde concentrations. (p. 58)                                 |
| 4  |              | $\infty$ | Reconciliation of divergent statements regarding systemic delivery of formaldehyde,           |
| 5  |              |          | (p.59) as direct evidence of systemic delivery of formaldehyde is generally lacking. $(p.5)$  |
| 6  |              | $\infty$ | Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic       |
| 7  |              |          | effects at distant sites. (p. 5)                                                              |
| 8  |              |          |                                                                                               |
| 9  | $\infty$     | Do       | se-Response Assessment                                                                        |
| 10 |              | $\infty$ | Independent analyses of the dose-response models to confirm the degree to which the           |
| 11 |              |          | models fit the data appropriately. (p. 14)                                                    |
| 12 |              | $\infty$ | Consideration of the use of alternative extrapolation models for the analysis of the          |
| 13 |              |          | cancer data. (p.14)                                                                           |
| 14 |              | $\infty$ | Further justification of the selection and use of the NCI cohort (Beane Freeman, et al.       |
| 15 |              |          | 2009) for calculation of unit risk because the cumulative exposure metric (used in the        |
| 16 |              |          | calculation of unit risk) was not related to leukemia risk in the NCI cohort. (p. 112)        |
| 17 |              |          |                                                                                               |
| 18 | $\infty$     | Me       | ethods for Evidence Integration                                                               |
| 19 |              | $\infty$ | Development of an approach to weight of evidence that includes "a single integrative          |
| 20 |              |          | step after assessing all of the individual lines of evidence". Although a synthesis and       |
| 21 |              |          | summary are provided, the process that EPA used to weigh different lines of evidence          |
| 22 |              |          | and how that evidence was integrated into a final conclusion are not apparent in the          |
| 23 |              |          | draft assessment and should be made clear in the final version. (p. 113)                      |
| 24 | A summary    | of e     | each of these recommendations and data gaps, along with the new science that has been         |
| 25 | conducted    | to a     | ddress them is provided in Table 2 and discussed in the following sections.                   |
| 26 |              |          |                                                                                               |
|    |              |          |                                                                                               |
| 27 | 3.1 Epidem   | niolo    | ogical Evidence                                                                               |
| 28 | The NRC Po   | eer F    | Review called attention to the EPA's sole reliance on epidemiological studies to determine    |
| 29 | causality, r | athe     | er than integrating epidemiology data with the toxicological and mechanistic evidence.        |
| 30 | When infe    | ring     | g causation from epidemiology studies, the evidence is critically assessed and synthesized    |
| 31 | across a bo  | dy c     | of individual studies, with greater weight assigned to studies of higher quality (rather than |
| 32 | assigning e  | qual     | I weight to each). Better epidemiological studies are those that implement individual         |
| 33 | level expos  | ure      | data, and minimize the potential for systematic bias and confounding. The                     |
| 34 | ascertainm   | ent      | of outcome and analysis using accurate (and specific) diagnosis are also critical in the      |



| 1  | causal evaluation. NRC noted that the grouping of "all LHPs" comprises 14 biologically distinct diagnoses |
|----|-----------------------------------------------------------------------------------------------------------|
| 2  | in humans and should not be used in determinations of causality. There is some evidence that these        |
| 3  | diseases may originate from the same stem cell line (Gluzman, et al. 2015; Goldstein 2010) and could      |
| 4  | therefore arise from direct effects on these cells. There are no studies, however, that demonstrate an    |
| 5  | effect on these stem cells following exposure to formaldehyde. The largest population of these stem       |
| 6  | cells would be found in the bone marrow, and, based on the available evidence, inhaled formaldehyde       |
| 7  | appears incapable of reaching the bone marrow (see Section 3.3.2). The affected cells would need to be    |
| 8  | circulating stem cells that encounter formaldehyde at the portal of entry (i.e., the nose or upper        |
| 9  | airways) and then return to the bone marrow.                                                              |
| 10 |                                                                                                           |
| 11 | After the NRC Peer Review was published, Checkoway et al. (2012) critically reviewed the                  |
| 12 | epidemiological evidence and reported inconsistent and sporadic associations between formaldehyde         |
| 13 | exposure and various specific LHM, including ML and only a few considering AML specifically. Since the    |
| 14 | critical review (Checkoway, et al. 2012), several additional epidemiological studies have been published  |
| 15 | that provide insights on formaldehyde exposure and AML risk and address other specific issues raised by   |
| 16 | the 2011 NRC Peer Review. The key strengths and limitations of these studies are highlighted below.       |
| 17 |                                                                                                           |
| 18 | 3.1.1 Key studies and their strengths and limitations                                                     |
| 19 | Since the update of mortality in the US formaldehyde users and producers cohort (Beane Freeman, et al.    |
| 20 | 2009), two other large industrywide cohort mortality studies have been updated: the NIOSH garment         |
| 21 | workers (Meyers, et al. 2013) and the UK industry-wide formaldehyde producers and users (Coggon, et       |
| 22 | al. 2014). In addition, a large population-registry-based case-control study of incident AML cases in the |
| 23 | Nordic countries, a small occupational study in Italy and a large multicenter European study of           |



| 1 | occupational exposures in a cohort established to study nutritional and metabolic risk factors in cancer |
|---|----------------------------------------------------------------------------------------------------------|
| 2 | risks have been published (Pira, et al. 2014; Saberi Hosnijeh, et al. 2013; Talibov, et al. 2014).       |

| 4 | NIOSH | cohort | study | of | garment | workers |
|---|-------|--------|-------|----|---------|---------|
|   |       |        |       |    |         |         |

| 5  | Meyers et al. (2013) updated mortality from 1960 through 2008 for 11,043 US garment workers exposed     |
|----|---------------------------------------------------------------------------------------------------------|
| 6  | to formaldehyde who worked for at least three months between 1955 and 1983 at three US factories. A     |
| 7  | total of 36 leukemia deaths was reported (SMR=1.04, 95% CI 0.73 - 1.44, compared to US mortality        |
| 8  | rates), of which 21 were ML (14 AML, 5 chronic myeloid leukemia (CML), 2 other and unspecified ML).     |
| 9  | Although this study did not link quantitative estimates of formaldehyde exposure to study subjects, an  |
| 10 | industrial hygiene survey during the early 1980s reported that formaldehyde concentrations were         |
| 11 | similar across all departments and facilities, and the overall geometric mean was 0.15 ppm with a       |
| 12 | geometric standard deviation of 1.90 (Stayner, et al. 1988). The formaldehyde resins used to treat      |
| 13 | permanent press fabrics had been reformulated over time, and as a result, the formaldehyde              |
| 14 | concentrations measured in the early 1980s were believed to be lower than the approximately 4 ppm       |
| 15 | estimated by NRC for years prior to 1970 (NRC 2014b). Meyers et al. (2013) reported an SMR for AML of   |
| 16 | 1.22 (95% CI 0.67 - 2.05), noting that they "continue to see limited evidence of an association between |
| 17 | formaldehyde and leukemia" and that "the extended follow-up did not strengthen previously observed      |
| 18 | associations." All 14 AML occurred 20 or more years after first exposure to formaldehyde. The NIOSH     |
| 19 | study is a large cohort with adequate follow up but limited industrial hygiene measurements of          |
| 20 | historical formaldehyde concentrations, as most were first exposed prior to 1970. Therefore, the study  |
| 21 | did not assign individual estimates of cumulative or peak exposure, and analyses for mortality due to   |
| 22 | various LHM including AML were performed by duration of exposure. Information on smoking was also       |
| 23 | lacking.                                                                                                |
|    |                                                                                                         |



| 1  | Registry-based case control study of AML in Nordic countries                                              |
|----|-----------------------------------------------------------------------------------------------------------|
| 2  | Talibov et al. (2014) analyzed 15,332 incident cases of AML diagnosed in Finland, Norway, Sweden, and     |
| 3  | Iceland from 1961 to 2005. The investigators matched 76,660 controls by year of birth, sex, and           |
| 4  | country. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate        |
| 5  | quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen             |
| 6  | between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure      |
| 7  | to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene |
| 8  | chloride, perchloroethylene, other organic solvents) and radiation (hazard ratio (HR) 0.89, 95% CI 0.81 - |
| 9  | 0.97 for workers exposed to ≤0.171 ppm-years; HR 0.92, 95% CI 0.83 -1.03 for workers exposed to 0.171     |
| 10 | - 1.6 ppm-yrs, and HR 1.17, 95% CI 0.91 - 1.51 for > 1.6 ppm-years, compared to workers not exposed to    |
| 11 | formaldehyde). The strengths of this study were its exposure assessment based on a validated job          |
| 12 | exposure matrix (JEM) and the comprehensive ascertainment of incident (not mortality) AML cases,          |
| 13 | resulting in high statistical power to detect increased risks and the ability to consider and control for |
| 14 | other possible leukemogens. One major limitation is the lack of data on smoking, which also is known to   |
| 15 | cause leukemia. This study failed to find an association between benzene and AML; however, risk of        |
| 16 | AML may be limited to very high concentrations that historically occurred only in a few occupational      |
| 17 | settings, e.g., the rubber hydrochloride industry (Infante, et al. 1977; Schnatter, et al. 2012).         |
| 18 |                                                                                                           |
| 19 | European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study                          |
| 20 | Saberi Hosnijeh et al. (2013) followed 241,465 subjects from 1992 through 2010 for a prospective study    |
| 21 | of lymphoid and myeloid leukemia risk in relation to occupation, nutrition and metabolic risk factors.    |
| 22 | The European Prospective Investigation into Cancer (EPIC) investigators studied occupational risk factors |
| 23 | among 477 incident leukemia cases (201 ML, including 113 AML, and 237 lymphoid leukemia) in France,       |
|    |                                                                                                           |



24

Oxford (UK), the Netherlands, Sweden, Norway, and Italy (Saberi Hosnijeh, et al. 2013). Occupational

| 1  | exposures were estimated using a general population job exposure matrix that classified occupational    |
|----|---------------------------------------------------------------------------------------------------------|
| 2  | codes of study subjects into categories of high, low, and no exposure for 11 specific agents (e.g.,     |
| 3  | benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). However, the  |
| 4  | authors note that work histories were missing on a large number of cohort member, and these             |
| 5  | individuals had to be excluded, and lacking detail on others but that these effects would be non-       |
| 6  | differential, attenuating risk estimates. On the other hand, this is one of the few studies examining   |
| 7  | specific subtypes of leukemia adjusted for smoking (as well as alcohol consumption, age at recruitment, |
| 8  | sex, and country). AML risk was not increased among the low formaldehyde exposure group (HR 1.01,       |
| 9  | 95% CI 0.65 - 1.57) after adjusting for sex, smoking status, alcohol intake, age at recruitment and     |
| 10 | country, and no AML cases occurred among individuals in the high-exposure category. An HR for chronic   |
| 11 | lymphocytic leukemia of 1.45 (95% CI 0.46 - 4.56) was reported among those with high exposure to        |
| 12 | formaldehyde, but this was based on 3 or fewer cases. ML risks were increased among those employed      |
| 13 | in chemical laboratories and shoe and leather workers, and weakly increased among those exposed to      |
| 14 | benzene but not those exposed to ionizing radiation (Saberi Hosnijeh et al. 2013).                      |
| 15 |                                                                                                         |
| 16 | UK formaldehyde users and producers cohort study                                                        |
| 17 | Coggon et al. (2014) updated mortality through 2012 for the UK cohort of 14,008 formaldehyde users      |
| 18 | and producers; however, the analysis grouped all ML and did not analyze AML mortality separately.       |
| 19 | Similar to other large industrial cohorts (Beane Freeman, et al. 2009; Meyers, et al. 2013), industrial |
| 20 | hygiene measurements were not available in the early years and investigators estimated averages for     |
| 21 | job titles based on irritant symptoms and later measurements. Exposures were estimated to range from    |
| 22 | background (< 0.1 ppm), low exposure (0.1 - 0.5 ppm), moderate exposure (0.6 - 2.0 ppm) and high        |
| 23 | exposure (> 2 ppm). These exposure categories were similar to those estimated by Stewart et al. (1986)  |
| 24 | and applied in Beane Freeman et al. (2009). Moreover, a larger proportion (and greater number) of the   |



| 1  | UK cohort was exposed to high concentrations of formaldehyde (approximately 18% of the cohort) than        |
|----|------------------------------------------------------------------------------------------------------------|
| 2  | the US cohort (approximately 4% of the cohort). Coggon et al. 2014 reported no increased mortality         |
| 3  | from ML (SMR 1.16, 95% CI 0.60 -2.20 for background exposure; SMR=1.46, 95% CI 0.84 - 2.36 for             |
| 4  | low/moderate exposure; and SMR 0.93, 95% CI 0.450 -1.82 for high exposure). In a nested case-control       |
| 5  | analysis of 45 ML (diagnosis from underlying or contributing cause of death or as a cancer registration)   |
| 6  | and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen.         |
| 7  | Although ML risk was non-statistically significantly increased among workers exposed to high               |
| 8  | concentrations for < 1 year (OR=1.77, 95% CI 0.45 - 7.03), workers exposed to high concentrations $\geq 1$ |
| 9  | year showed no increased risk (OR 0.96, 95% CI 0.24 - 3.82) (Coggon, et al. 2014).                         |
| 10 |                                                                                                            |
| 11 | Extended analysis of the NCI cohort study to evaluate specific types of myeloid leukemia                   |
| 12 | Checkoway et al. (2015) obtained the data from the NCI formaldehyde industrial workers cohort to           |
| 13 | further investigate specific types of leukemias, including AML (which had never been reported for this     |
| 14 | cohort), as well as performing an alternative analysis of peak exposure. The investigators reported that   |
| 15 | AML mortality was unrelated to cumulative exposure or peak exposure. Twelve of 34 AML deaths and 6         |
| 16 | of 13 CML deaths occurred among study subjects with less than one year of employment. For workers          |
| 17 | employed at least one year, the risk of AML was highest (but not statistically significant) among workers  |
| 18 | with peak exposures of ≥2.0 to <4 ppm (HR 1.78, 95% CI 0.61-5.25) and no trend was seen with               |
| 19 | increasing category of peak exposure (p for trend 0.37). In contrast, CML risks were greater although      |
| 20 | the estimates were imprecise (HR 4.83, 95% CI 0.64-36.42 for peak exposure ≥2.0 to <4 ppm based on 2       |
| 21 | CML deaths and HR 5.32, 95% CI 0.81-34.90 for peak exposure ≥4 ppm based on 2 CML deaths).                 |
| 22 |                                                                                                            |
| 23 | 3.1.2 Synthesis of epidemiology studies: Exposure assessment issues identified by NRC                      |



| 1                                                | One of the major issues nightighted by the NRC peer review is that one exposure metric (peak exposure)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2                                                | was used to determine causality in the draft IRIS assessment, while a different exposure metric                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 3                                                | (cumulative exposure) was used for the dose-response evaluation to calculate an inhalation unit risk.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 4                                                | The NRC (2011) review of the Draft IRIS Assessment stated "the reliance on the peak exposure metric to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 5                                                | determine causality rather than the more conventional dose metric of cumulative exposure should be                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 6                                                | further justified particularly in the absence of established modes of action" [p.112]. NRC further                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 7                                                | elaborated:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 8<br>9<br>10<br>11<br>12<br>13<br>14<br>15<br>16 | "In the absence of evidence regarding exposure-disease mechanisms, as in the case of formaldehyde and LHP cancers, cumulative exposure is typically the default dose metric applied in epidemiologic analyses and risk assessment. But the most significant results were found for peak exposures, which have the greatest associated uncertainty. In view of the importance of this study, EPA should clarify the basis of its interpretations of the results regarding the various dose metrics and the various LHP cancers. Despite those concerns, the committee agrees that the NCI study is the most appropriate available to carry forward for calculation of the unit risk." (pp. 112-113) |
| 17                                               | The NRC recommended that the quality of exposure assessment relied upon in epidemiological                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 18                                               | evaluations should be explicitly evaluated when weighting and synthesizing epidemiological evidence.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 19                                               | Where known causal relationships have been observed, exposure-response relationships often are seen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 20                                               | with various exposure metrics, with stronger associations seen when more relevant metrics and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 21                                               | exposure time windows are examined. Results such as those reported by Beane Freeman et al. (2009)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 22                                               | are a good example of conflicting findings: the conventional exposure metric, cumulative exposure,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 23                                               | demonstrated no association with risk of ML, whereas a surrogate of 'peak' exposure suggested one                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 24                                               | (Beane Freeman 2009). When evaluating differences between cumulative exposure and peak exposure,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 25                                               | and comparing risks associated with these, several differences should be highlighted.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 26                                               | NCI investigators (Beane Freeman, et al. 2009; Blair, et al. 1986; Hauptmann 2003) defined peak                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 27                                               | exposure as the maximum peak, and the NCI investigators substituted the time-weighted average (TWA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 28                                               | for jobs without assigned peak exposures (Stewart, et al. 1986). The authors reported a significant test                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |



| Τ  | for trend between peak formaldenyde exposure and leukemia, but only when unexposed subjects were                                              |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------|
| 2  | included. Increased risk was not seen for higher peak exposure categories (2.0 to <4.0 ppm, or $\geq$ 4.0                                     |
| 3  | ppm) when compared to the lower peak category (>0 to <2.0 ppm). No association was reported with                                              |
| 4  | frequency of peak exposure, average intensity of exposure or with cumulative exposure to                                                      |
| 5  | formaldehyde ("There was little evidence among formaldehyde workers of association for any                                                    |
| 6  | lymphohematopoietic malignancy (LHM) with average intensity or cumulative exposure."). In fact, a                                             |
| 7  | 10% deficit of ML deaths (acute and chronic types combined) was reported when compared to US                                                  |
| 8  | population mortality rates. In an internal analysis, Beane Freeman et al. (2009) reported that ML deaths                                      |
| 9  | were not associated with the number or frequency of peaks. If there were a true association between                                           |
| 10 | peak exposure and leukemia, one would expect to see an association with number of peaks and not only                                          |
| 11 | ever having a (perhaps a single) peak exposure. Hauptmann et al. (2003) acknowledge that "no                                                  |
| 12 | measurements of peak exposure were available in this study. Peak exposures were therefore estimated                                           |
| 13 | by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-                                             |
| 14 | weighted average" (Hauptmann et al. 2003, p. 1616; Stewart, et al. 1986). Stewart et al. (1986) reported                                      |
| 15 | that the exposure reconstruction included rating confidence (i.e., confident, less confident, not                                             |
| 16 | confident) in the exposure estimate; however, the "confidence" category appeared to apply to the                                              |
| 17 | "rank" exposure and not the "peak exposure." For example, if an IH specified "not confident" for an                                           |
| 18 | average exposure estimate, it is not clear how or if this information applied to the estimate of peak                                         |
| 19 | exposure (categorized during data collection as $1 = \text{none}$ , $2 = 0.1 - 0.5$ , $3 = 0.51 - 2.0$ , $4 = 2.1 - 4.0$ , $5 = > 0.51 - 2.0$ |
| 20 | 4.0, 9 = unknown) (Stewart, et al. 1986).                                                                                                     |

In extended analyses of the NCI cohort study, Checkoway et al. (2015) refined the classification of peak

exposure. Workers who did not work in jobs identified as likely having peak exposures were classified as

not peak-exposed, and became the referent group. A total of 3,478 cohort members were classified as

having worked in jobs with estimated peak exposure of 2-<4 ppm, and 2,907 worked in jobs with





21

22

23

| 1 | estimated peak exposure of | f ≥4 ppm. | Analysis by | ML subtype (i.e., | AML and CML | deaths, separately) |
|---|----------------------------|-----------|-------------|-------------------|-------------|---------------------|
|   |                            |           |             |                   |             |                     |

- 2 found no association between peak exposure and AML mortality (HR 1.71, 95% CI 0.72 4.07 and HR
- 3 1.43, 95% CI 0.56 3.63, respectively) (Checkoway, et al. 2015). However, 13 of the 34 AML deaths were
- 4 classified as having worked in jobs likely having peak exposure >2.0 ppm, only 4 of which worked in
- 5 these jobs within the 20 years preceding their AML death (i.e., latest exposure), and only one occurred
- 6 (similar to the number expected) within the typical AML latency window of 2 to 15 years. Upon fuller
- 7 analyses of these data, Checkoway et al. (2015) subsequently found that only a third of all the AML
- 8 deaths were among cohort members assigned to categories with any peak exposure (i.e., >2.0 ppm),
- 9 nearly all of whom had their last peak exposure more than 20 years earlier, well outside of the
- 10 maximum latency window.
- 11 Coggon et al. (2014) also reported that limited IH data were available for the UK formaldehyde users and
- 12 producers cohort, preventing the derivation of quantitative metrics. Nevertheless, the investigators
- 13 expressed high confidence that the high exposure category corresponded to average concentrations of
- 14 at least 2 ppm. Industrial hygiene data also were limited in the US NCI industrial workers study,
- 15 although the investigators used them as part of a detailed exposure reconstruction using best practices
- for such a reconstruction at the time. Stewart, et al. (1986) reported that historical exposure levels
- 17 were estimated because most companies did not begin sampling until the mid-1970's: they also
- 18 monitored "present day" (i.e., early 1980's) operations to help extrapolate historical exposures. The NCI
- investigators relied up exposure rank (six levels of TWA): trace, < 0.1 ppm, 0.1 0.5 ppm, 0.51- 2.0 ppm
- 20 and > 2 ppm.
- 21 One criticism leveled at the UK worker cohort study (Acheson, et al. 1984; Coggon, et al. 2003, 2014;
- 22 Gardner, et al. 1993) was that the "authors reported a concern about the quality of data when they
- 23 made exposure assignments" (NRC 2014b). This criticism seems to stem from the appropriate
- identification and discussion of study limitations by earlier UK investigators: Gardner et al. (1993)



| 1  | reported "when jobs were being placed into qualitative categories of exposure in the British study, some  |
|----|-----------------------------------------------------------------------------------------------------------|
| 2  | disagreement occurred as to which of two adjacent grades was most appropriate-for example, high or        |
| 3  | moderate? To achieve consistency across all the factories, the higher of the two was always used. It is   |
| 4  | not clear how differences were resolved in the United States study." Thus, there are no essential         |
| 5  | differences in the approach used by the UK investigators and the US investigators: both studies           |
| 6  | reported that limited data were available on quantitative exposure measures using existing industrial     |
| 7  | hygiene data (from the 1980s); both classifications allowed for the consideration of changes in processes |
| 8  | and exposure controls during the period of the study; and both used ranked categories of exposure,        |
| 9  | developed before the estimation process, based somewhat on subjective sensory experiences                 |
| 10 | encountered in the job (e.g., odor occasionally present), and both used eye irritation and odor           |
| 11 | throughout the day to identify the highest intensity of exposure jobs (Acheson, et al. 1984; Stewart, et  |
| 12 | al. 1986).                                                                                                |
| 13 | Ultimately, the Beane Freeman et al. (2009) study alone does not (and cannot) provide reliable support    |
| 14 | for a conclusion that peak formaldehyde exposure causes ML or AML, especially considering the             |
| 15 | absence of peak measurement data in the US study, the results of the re-analysis by Checkoway et al.      |
| 16 | (2015), and the updated results from the UK study (Coggon, et al. 2014), which used a more                |
| 17 | conservative approach to exposure estimation.                                                             |
| 18 |                                                                                                           |
| 19 | 3.1.3 Synthesis of Epidemiology Studies: Evaluation of the Most Specific Diagnosis                        |
| 20 | The NRC (2011) raised the issue that diverse types of leukemias and lymphomas should not be grouped       |
| 21 | "because it combines many diverse cancers that are not closely related in etiology and cells of origin.   |
| 22 | Although the draft IRIS assessment explores specific diagnoses—such as AML and CML, as well as            |
| 23 | Hodgkin lymphoma and multiple myeloma (see, for example, EPA 2010, Table 4-92)—the                        |
| 24 | determinations of causality are made for the heterogeneous groupings of "all LHP cancers," "all           |



| 1  | leukemias," and "ML". When results for heterogeneous groupings are presented, there is no evidence            |
|----|---------------------------------------------------------------------------------------------------------------|
| 2  | of increased risk of all LHP cancers (Meyers, et al. 2013; Bean Freeman, et al. 2009) or all leukemias        |
| 3  | combined (Coggon et al. 2014; Meyers et al. 2013; Beane Freeman, et al., 2009) in industrial cohorts          |
| 4  | when compared to general mortality rates. In addition, there is no evidence of exposure-response              |
| 5  | associations between all LHPs combined (or all leukemias combined) and cumulative exposure or                 |
| 6  | average exposure (Beane Freeman, et al. 2009) or duration of exposure (Meyers, et al., 2013; Coggon, et       |
| 7  | al., 2014).                                                                                                   |
|    |                                                                                                               |
| 8  | Interestingly, the EPA IRIS Draft (2010) noted that "Acute leukemias (ALL and AML), believed to arise         |
| 9  | from transformation of stem cells in the bone marrow, are less plausible. In contrast chronic lymphatic       |
| 10 | leukemia, lymphomas, multiple myelomas (from plasma B cells), and unspecified cancers may involve an          |
| 11 | etiology in peripheral tissues to include cells, cell aggregates, germinal centers, and lymph nodes. An       |
| 12 | association of these cancers to an exogenous agent acting at the POE [portal of entry] is biologically        |
| 13 | plausible" (page 4-190).                                                                                      |
|    |                                                                                                               |
| 14 | While the etiologies of most LHM are poorly understood, the possible role of environmental agents is          |
| 15 | plausible for AML, which has been linked with benzene, tobacco smoking, ionizing radiation and various        |
| 16 | cancer treatment agents, such as cisplastin, all of which have been classified by IARC as known human         |
| 17 | carcinogens that cause AML. It should stressed, however, that evidence exists that these agents, or           |
| 18 | their carcinogenic components, are capable of reaching the bone marrow. However, only six                     |
| 19 | epidemiological studies of workers substantially exposed to formaldehyde published to date have               |
| 20 | published AML-specific results (Blair, et al. 2001; Checkoway, et al. 2015; Hauptmann, et al. 2009;           |
| 21 | Meyers, et al. 2013; Saberi Hosnijeh, et al. 2013; Talibov, et al. 2014), four of which were not available at |
| 22 | the time of the IARC review or the release of the EPA IRIS Draft. Saberi Hosnijeh et al. (2013) reported      |
| 23 | no association between "low" formaldehyde exposure and incidence of myeloid leukemia HR 1.02, 95%             |
| 24 | CI 0.72-1.42 based on 49 cases exposed to formaldehyde and 130 unexposed cases). No differences               |



| 1        | were seen between subtypes: AML (HR 1.01, 95% CI 0.65 - 1.57) or CML (HR 0.92, 95% CI 0.46-1.84). No                                                                                               |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2        | myeloid case (and therefore no AML cases or CML cases) occurred among those classified as having                                                                                                   |
| 3        | "high" formaldehyde exposure (Saberi Hosnijeh, et al. 2013). Talibov et al. (2014) found no association                                                                                            |
| 4        | between formaldehyde and incident AML, after adjusting for exposure to specific solvents and ionizing                                                                                              |
| 5        | radiation (HR 1.17, 95% CI 0.91-1.51 for 136 workers and 628 controls exposed to > 1.6 ppm-yrs).                                                                                                   |
| 6        | Meyers et al. (2013) reported a SMR for AML of 1.22 (95% CI 0.67-2.05) based on 14 observed AML                                                                                                    |
| 7        | deaths. Checkoway et al. (2015) performed AML-specific analysis using the NCI cohort, which had                                                                                                    |
| 8        | provided results only for all ML combined (Beane Freeman, et al. 2009). When compared to US referent                                                                                               |
| 9        | rates, AML mortality risk was found to be decreased among workers exposed to formaldehyde (SMR                                                                                                     |
| 10       | 0.80, 95 %CI 0.46 - 1.14) and internal analysis of exposure reported no trend with increasing cumulative                                                                                           |
| 11       | exposure or peak exposure categories (Checkoway, et al. 2015). Thus, new analyses of the NCI                                                                                                       |
| 12       | formaldehyde workers cohort specifically for AML detract from the hypothesis that formaldehyde                                                                                                     |
| 13       | causes AML.                                                                                                                                                                                        |
| 14       | The associations reported by Beane Freeman et al. (2009) between formaldehyde exposure and Hodgkin                                                                                                 |
| 15       | lymphoma and CML have not been observed in other studies (Meyers, et al. 2013; Saberi Hosnijeh, et al.                                                                                             |
| 16       | 2013); and are less plausible, given the lack of known associations with CML and other chemicals or                                                                                                |
| 17       | agents, such as benzene (Checkoway, et al. 2015). Saberi Hosnijeh et al. (2013) reported a RR of 0.92                                                                                              |
| 18       | (95% 0.46 to 1.84) based on 46 CML cases. Meyers et al. (2013) reported a SMR of 1.35 (95% CI 0.44-                                                                                                |
| 19       | 3.15), based on 5 CML cases through 2008. The absence of established toxicological mechanisms for                                                                                                  |
|          |                                                                                                                                                                                                    |
| 20       | formaldehyde exposure and any of the LHM further weakens arguments for causation (Checkoway, et                                                                                                    |
| 20<br>21 | formaldehyde exposure and any of the LHM further weakens arguments for causation (Checkoway, et al. 2012, 2015), especially given that inhaled formaldehyde appears incapable of reaching the bone |



### 1 3.2 Toxicological Evidence

- 2 3.2.1 Animal Evidence of Formaldehyde-Induced LHM
- 3 With regard to animal evidence of formaldehyde-induced LHM, the EPA (2010) IRIS document indicated
- 4 that the available animal evidence is limited, discussing mainly the results from the Battelle Columbus
- 5 Laboratories (1981) study. The EPA (2010) IRIS document indicates that this study provides the only
- 6 evidence of formaldehyde-induced LHM in animal models. However, the NRC (2011) Committee
- 7 indicated that although intriguing, EPA's unpublished re-analysis of the Battelle chronic experiments in
- 8 mice and rats (Battelle Columbus Laboratories 1981) contributes little to the weight of evidence
- 9 evaluation.
- 10 In rats, Battelle Columbus Laboratories (1981) reported the incidence of leukemia (most of which were
- 11 diagnosed as undifferentiated leukemia found sporadically in various organs) in male and female Fischer
- 12 344 rats following exposure to concentrations of 0, 2, 6, or 15 ppm for 24 months, followed by 6 months
- with no exposure. No concentration-related increases in the incidences of leukemia in either sex of rats
- 14 were reported by Battelle Columbus Laboratories (1981), when a standard Fisher-Irwin exact test was
- 15 applied (males p=0.0972; females p=0.2316).
- 16 Because of a significant number of early deaths in the high concentration group of both males and
- 17 females, Battelle Columbus Laboratories (1981) also applied Tarone's extension to the Cox log-rank test
- 18 (Tarone 1975) to evaluate the leukemia incidence data. This test accounts for the number of animals at
- 19 risk at each time point when the response of interest is observed. This adjustment assessed the
- 20 probability of developing the endpoint of interest in those animals that did not survive until the
- 21 termination of the study. The results of Tarone's extension indicated that the incidence among female



- 1 rats in the high concentration group were statistically significant (p=0.0056, not 0.0003 as reported<sup>3</sup>);
- 2 however, no association was seen in the male rats exposed at high concentrations (p=0.6891). No
- 3 concentration-related increase in leukemia was observed in the female rates exposed at 2 ppm or 6
- 4 ppm, and no survival problems were noted. Even after application of Tarone's extension, all leukemia in
- 5 male or female rats was not identified in the Battelle Columbus Laboratories (1981) study as an
- 6 endpoint related to formaldehyde exposure, nor was it so designated in two publications citing this
- 7 study (Kerns, et al. 1983; Swenberg, et al. 2012).
- 8 More contemporary, statistical methods, such as the Cochran-Armitage and the Poly3 (Bailer and Portier
- 9 1988; Peddada and Kissling 2006) trend tests, have replaced those used in the early 1980's. The Poly3
- 10 trend test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear
- 11 trend test to take inter-group survival differences into account. Importantly, the Poly3 test is the test
- 12 currently used by the National Toxicology Program (NTP) to evaluate incidence data both for trend and
- 13 pair-wise comparisons, to assess the probability of the response in the presence of inter-current
- mortality. The results of the application of these tests indicated p values of 0.43 and 0.82 for the Poly3
- and Cochran-Armitage, respectively, demonstrating no association.
- 16 In mice, the EPA (2010) Draft IRIS Assessment suggests that the "adjusted" incidence of lymphoma in
- 17 female mice, when the 6-month sacrifice animals were removed from consideration (because tissues
- outside of the respiratory tract were not examined), was statistically significant (p<0.05) in animals
- 19 exposed to 15 ppm formaldehyde, compared to untreated controls. However, as indicated in the
- 20 methods for the Battelle Columbus Laboratories (1981) study, statistical significance, when applying the
- 21 Tarone extension of the Cox test, is achieved with a p value of p=0.05 divided by the number of dose



<sup>&</sup>lt;sup>3</sup> This appears to be a misreading of the Battelle report. In the Battelle Report Volume A Table 10 – Analysis of Effects of Formaldehyde in Female Rats - reports a p-value of 0.0056 from the Adjusted Cox/Tarone pair-wise comparison of the control to 15 ppm for Leukemia, all. The next row in that table with an endpoint of Uterus, Endometrial Stromal Polyp is the one that reports a p-value of 0.0003 for the pair-wise analysis of control to 15 ppm.

- groups. In the case of the Battelle Columbus Laboratories (1981) study for the mouse data, statistical
- 2 significance would be p<0.0167, as noted in the summary tables (Table 8 of the Battelle Columbus
- 3 Laboratories (1981) report); therefore, based on this criterion, this endpoint was not considered
- 4 statistically significant. As with the leukemia incidence in rats, the Battelle study authors did not report
- 5 lymphoma in mice as an endpoint related to formaldehyde exposure.
- 6 Since 2010, two short-term carcinogenicity studies have been conducted and published (as a Technical
- 7 Report) by the NTP of NIEHS in strains of genetically predisposed mice (male C3B6.129F1-
- 8 Trp53tm1Brdp53 haplo-insufficient mice and male B6.129-Trp53tm1Brd) (Morgan, et al. 2017). These
- 9 short-term carcinogenicity studies were conducted to test the hypothesis that formaldehyde inhalation
- 10 would result in an increased incidence and/or shortened latency to hasal and lymphohematopoietic
- 11 tumors in and to investigate hypotheses that formaldehyde may induce leukemia by a mechanism not
- 12 involving DNA adduct formation. This proposed mechanism assumes that inhaled FA could cause
- significant genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels.
- 14 These damaged stem cells could reach the general circulation, home to tissues that support the
- 15 hematopoietic niche, undergo lodgement and become leukemic stem cells. The animals were exposed
- to 7.5 or 15 ppm formaldehyde 6hr/day, 5 days/wk, for 8 weeks. The investigators reported that
- 17 because the doubling time for hematopoietic stem and progenitor cells (HSPCs) is between 2 and 4
- 18 weeks, and the entire HSPC pool turns over every 8 weeks, an 8 week exposure duration was considered
- 19 sufficient to investigate the hypothesized mechanism for inducing leukemia. Following the 8-wk
- 20 inhalation exposure, mice were monitored for approximately 32 weeks (until approximately 50 weeks of
- 21 age). At the highest concentrations, significant cell proliferation and squamous metaplasia of the nasal
- 22 epithelium were observed; however, no nasal tumors were observed. No cases of leukemia were seen
- 23 in either strain and a low incidence of lymphoma in exposed mice was not considered related to
- 24 exposure. In addition, no significant changes in hematological parameters were noted. Under the



| 1        | conditions of these studies, the authors concluded that formaldehyde inhalation did not cause leukemia                               |  |  |  |  |
|----------|--------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|
| 2        | in these strains of genetically predisposed mice (Morgan et al. 2017).                                                               |  |  |  |  |
| 3        | Overall, the weight of evidence from animal studies in 2010 did not support an association between                                   |  |  |  |  |
| 4        | formaldehyde exposure and LHM. Since that time, additional studies (Morgan, et al. 2017) have                                        |  |  |  |  |
| 5        | provided evidence that suggests a lack of association between formaldehyde exposure and LHM. In                                      |  |  |  |  |
| 6        | addition, no evidence of changes in blood parameters that might be associated with leukemias has been                                |  |  |  |  |
| 7        | reported in any animal studies exposed to formaldehyde at high concentrations following both acute                                   |  |  |  |  |
| 8        | and chronic durations (Appelman, et al. 1988; Dean, et al. 1984; Johannsen, et al. 1986; Kamata, et al.                              |  |  |  |  |
| 9        | 1997; Kerns, et al. 1983; Til, et al. 1988, 1989; Tobe, et al. 1989; Vargova, et al. 1993; Woutersen, et al.                         |  |  |  |  |
| 10       | 1987). Among these studies, Vargová et al. (1993) reported increased red blood cell counts and                                       |  |  |  |  |
| 11       | increased proportions of lymphocytes and monocytes in rats, rather than decreases, and this follows                                  |  |  |  |  |
| 12       | exposure to formaldehyde by gavage at 80 mg/kg/day for 28 days.                                                                      |  |  |  |  |
| 13       |                                                                                                                                      |  |  |  |  |
| 14       | 3.3 Mode of Action Evidence                                                                                                          |  |  |  |  |
| 15<br>16 | 3.3.1 Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations |  |  |  |  |
| 17       | NRC (2011) recommended that one key improvement to the science would be an understanding of                                          |  |  |  |  |
| 18       | when exogenous formaldehyde exposure altered normal endogenous formaldehyde concentrations.                                          |  |  |  |  |
| 19       | Because formaldehyde is an endogenously present compound, it is important to differentiate the                                       |  |  |  |  |
| 20       | presence of levels that are due to normal metabolic processes, from levels that might be present as a                                |  |  |  |  |
| 21       | result of exogenous exposure. A number of studies have applied sensitive methods to differentiate                                    |  |  |  |  |
| 22       | exogenous and endogenous levels of formaldehyde in tissues (Casanova-Schmitz, et al. 1984; Lu, et al.                                |  |  |  |  |



23

2010, 2011; Moeller, et al. 2011; Swenberg, et al. 2011).

- 1 The results of these studies with highly sensitive instruments and accurate assays indicate that inhaled
- 2 formaldehyde was present in the nasal respiratory epithelium, but not other tissues beyond the site of
- 3 initial contact. In contrast, endogenous adducts were readily detected in all tissues examined.
- 4 Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold
- 5 lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal
- 6 respiratory epithelium, respectively (Yu, et al. 2015).
- 7 An additional study conducted in rats with exposed to <sup>13</sup>C-formaldehyde (Kleinnijenhuis, et al. 2013)
- 8 provided results consistent with those from studies focused on measuring endogenous versus
- 9 exogenous DNA adducts. In this study, Sprague-Dawley rats were exposed nose-only to 10 ppm <sup>13</sup>C-
- 10 formaldehyde for 6 hours and blood concentrations evaluated during exposure and for 30 minutes
- following exposure. This study was conducted specifically to investigate the mechanism proposed by
- 12 Zhang et al. (2010) formaldehyde is absorbed during respiration and could reach any target tissue, such
- as the bone marrow, via the blood in the form of methanediol to exert its genotoxic activity. Exogenous
- 14 13C-formaldehyde was not detectable in the blood of rats either during or up to 30 min after the
- 15 exposure. The authors concluded that "it is highly unlikely that the mechanism proposed by Zhang et al.
- 16 (2009), that exposure to FA by inhalation may lead to an increased FA concentration in blood and as
- such may cause leukemia, is true" (Kleinnijenhuis, et al. 2013).
- 18 New studies have been conducted to investigate the potential toxicity/carcinogenicity of endogenous
- 19 formaldehyde. The most recent studies demonstrate that endogenous formaldehyde in bone marrow is
- toxic, and probably carcinogenic, and may increase leukemia risk (Gao, et al. 2017; Lai, et al. 2016).
- 21 3.3.2 Reconcile divergent statements regarding systemic delivery
- 22 Multiple studies in multiple species rats (Lu, et al. 2011; Yu, et al. 2015), monkeys (Moeller, et al. 2011;
- 23 Yu, et al. 2015), in vitro studies of human plasma (Edrissi, et al. 2013) conducted with a sensitive



- analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts have
- 2 demonstrated that inhaled exogenous formaldehyde is not systemically absorbed or reaches sites
- 3 distant from the point of initial contact. In addition to these studies, the available data on the
- 4 toxicokinetics of formaldehyde suggest that no significant amount of "free" formaldehyde would be
- 5 transported beyond the portal of entry.
- 6 In addition to studies supporting the lack of systemic delivery of formaldehyde, anatomically accurate
- 7 computational fluid dynamics (CFD) models of the rat, monkey, and human have been applied to
- 8 evaluate the effects of endogenously present formaldehyde on uptake from the respiratory tract. The
- 9 consideration of endogenous formaldehyde concentrations in nasal tissues did not affect flux or nasal
- uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted
- at lower exposure concentrations (Schroeter, et al. 2014).
- 12 3.3.3 Data are insufficient to conclude formaldehyde is causing cytogenetic effects at distant sites
- 13 The modes of action that have been proposed in the Draft IRIS Assessment to cause leukemogenesis rely
- strongly on the hypothesis that exposure to inhaled formaldehyde can result in cytogenetic effects at
- 15 sites distant from the portal of entry. While the NRC (2011) noted that numerous studies have shown
- 16 genotoxic effects in cells exposed *in vitro*, and a few studies have shown positive cytogenetic effects in
- 17 circulating blood lymphocytes in heavily-exposed workers, they also noted that it is unlikely that these
- 18 effects are relevant to a possible leukemogenic effect of formaldehyde, particularly at low exposure
- 19 levels. The potential leukemogenic effect and exposure-response relationships at lower exposure levels
- 20 have been comprehensively evaluated by Nielsen, et al. (2013, 2017).
- 21 One of the key studies cited in multiple agency evaluations as providing evidence of cytogenetic events
- in the development of leukemias is a study by Zhang et al. (2010). Zhang et al. (2010) compared the
- 23 prevalence of markers of hematopoietic function and chromosomal aneuploidy among workers



| 1  | occupationally exposed to formaldehyde with those of a group of unexposed workers in China. Ninety-          |
|----|--------------------------------------------------------------------------------------------------------------|
| 2  | four workers were included, with 43 workers occupationally exposed to formaldehyde and 51 workers            |
| 3  | unexposed to formaldehyde as controls. The authors reported a higher prevalence of monosomy 7 (loss          |
| 4  | of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures            |
| 5  | of CFU-GM colony cells. The authors suggested that this demonstrated that formaldehyde exposure was          |
| 6  | associated with an increase in leukemia-specific chromosomal aneuploidy in vivo in the hematopoietic         |
| 7  | progenitor cells of the exposed workers. However, no direct in vivo metaphases had been examined in          |
| 8  | workers blood. Furthermore, this was a cross-sectional comparison of blood and genetic measures              |
| 9  | between two groups, and observed differences could not be established as resulting from formaldehyde         |
| 10 | exposure or due to other overall differences between the two groups.                                         |
| 11 | Two re-analyses of the underlying data from the Zhang et al. (2010) study have been published (Gentry,       |
| 12 | et al. 2013; Mundt, et al. 2017). The first (Gentry, et al. 2013) relied upon selected underlying data       |
| 13 | provided through a Freedom of Information Act request that included: 1) individual data on blood cell        |
| 14 | counts in both formaldehyde-exposed and unexposed individuals including any data on health status of         |
| 15 | these individuals; 2) individual data on the FISH results for monosomy 7 and trisomy 8 for cultures of       |
| 16 | samples obtained from 10 formaldehyde-exposed workers and 12 unexposed controls; 3) data on                  |
| 17 | additional chromosomal abnormalities examined and/or observed; and 4) details of the methods                 |
| 18 | sufficient for a qualified scientist to replicate the results reported in the Zhang et al. (2010) study. The |
| 19 | results of this reanalysis suggested that factors other than formaldehyde exposure likely contributed to     |
| 20 | the effects reported. In addition, although the authors stated in their paper that "all scorable             |
| 21 | metaphase spreads on each slide were analyzed, and a minimum of 150 cells per subject was scored,"           |
| 22 | this protocol was not followed specifically for chromosome 7 or chromosome 8 (recent correspondence          |
| 23 | indicates a minimum of 150 total metaphases were scored for 24 chromosomes per subject). Far too             |
| 24 | few cells were counted to draw any meaningful conclusions, and far fewer than the approximately 400          |



- 1 per chromosome cited in previous analyses in which the protocol was described (Zhang et al. 2005;
- 2 Zhang et al. 2011). In addition, the assays used (CFU-GM) do not actually measure the proposed events
- 3 in primitive cells involved in the development of AML. Evaluation of these data indicates that the
- 4 aneuploidy measured could not have arisen *in vivo*, but rather arose during *in vitro* culture.
- 5 In 2014, Mundt et al. requested the individual exposure measurement data for each of the participants
- 6 in the Zhang et al. (2010) study from NCI. In 2016, the request was in part granted and the mean
- 7 formaldehyde estimate for each exposed worker (but not the individual exposure measurement values)
- 8 was provided via a Technology Transfer Agreement (TTA) with NCI. Using these data, the Gentry et al.
- 9 (2013) reanalysis was extended to include exposure-response analyses. Results of this second reanalysis
- 10 showed that differences seen at the group comparison level, i.e., comparing the prevalence of white
- 11 blood cell, granulocyte, platelet, and red blood cell counts at the group level in fact were independent of
- 12 measured formaldehyde exposure level. Among exposed workers, no association was observed
- 13 between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested
- by the original study authors to be indicators of ML risk. Differences between the two groups of
- 15 workers, other than formaldehyde exposure, were therefore likely to explain the results reported by
- 16 Zhang et al. (2010).
- 17 Subsequent studies of the same population of formaldehyde-exposed and non-exposed workers in
- 18 China (Lan, et al. 2015; Seow, et al. 2015; Bassig, et al. 2016) have been suggested by the authors to
- confirm the results of Zhang, et al. 2010; however, many of these studies report results from the same
- 20 biological samples as Zhang et al. (2010) and therefore, do not provide replication of the results. The
- repeated use of the original Zhang et al. (2010) data, and its implications, have been reiterated (Mundt,
- et al. 2017b (in press); Pira, et al. 2017; Gentry, et al. 2013; Speit, et al. 2010) and the original authors
- have responded to some of the criticisms (Rothman, et al. 2017; Lan, et al. 2015; Zhang, et al. 2010b).
- 24 Replication of the results of the Zhang et al. (2010) results will require replication in an independent



| 1  | population of formaldehyde-exposed workers, and where methodological issues are adequately               |
|----|----------------------------------------------------------------------------------------------------------|
| 2  | addressed. An attempt to replicate the results could be conducted in the same population of workers as   |
| 3  | Zhang, et al. (2010) and Lan, et al. (2015) in which the median exposures to 43 workers were 1.28 ppm    |
| 4  | (10th and 90th percentile: 0.63, 2.51 ppm). However, as noted previously (Section 3.1.1), no evidence    |
| 5  | of an association between formaldehyde exposure and leukemias have been reported in multiple recent      |
| 6  | epidemiological studies with large numbers of subjects that have been exposed to concentrations >2.0     |
| 7  | ppm. The increasing evidence that inhaled formaldehyde does not move beyond the portal of entry          |
| 8  | (Section 3.3.2) also calls into question many of the conclusions from the Zhang et al. (2010).           |
| 9  | Albertini and Kaden (2016) reviewed the body of data that reportedly indicates genetic changes in        |
| 10 | circulating blood cells and in blood-borne hematopoietic precursor cells (HPCs). These changes have      |
| 11 | been considered to be indicators that systemic genotoxicity does occur after human inhalation exposure   |
| 12 | to formaldehyde, although the mechanisms by which this could occur remain unknown. For each study,       |
| 13 | the authors examined the sources of exposure, possible co-exposures, biomarkers for internal exposures   |
| 14 | and genetic signatures of formaldehyde effects.                                                          |
| 15 | In reviewing the available studies, many genetic changes in blood cells were noted by Albertini and      |
| 16 | Kaden (2016), with a contrast in results between animal and human studies: the majority of animal        |
| 17 | studies were negative and the majority of human studies were positive. This pattern was attributed to    |
| 18 | the difference in target cell being studied, with bone marrow cells studied in animals and peripheral    |
| 19 | blood lymphocytes studied in humans. Exposure of human cells to formaldehyde at sites of contact in      |
| 20 | vivo could provide opportunities for exposure of T-lymphocytes to formaldehyde or products of            |
| 21 | oxidative stress, which could result in the genetic changes observed in peripheral blood cells. However, |
| 22 | these results are inconsistent with results from controlled animal studies, discussed previously, that   |
| 23 | demonstrate - by labeling and administered formaldehyde - inhaled (exogenous) formaldehyde does not      |
| 24 | travel beyond the portal of entry (Casanova-Schmitz, et al. 1984; Lu, et al. 2010, 2011; Moeller, et al. |



- 2011; Swenberg, et al. 2011). Therefore, these types of genetic changes reported in human studies do
- 2 not provide evidence that formaldehyde moves beyond the portal of entry to the bone marrow, which
- 3 would be necessary to result in direct induction of chromosome-level mutations in the bone marrow.
- 4 Despite the apparent inability of exogenous formaldehyde to reach the bone marrow, the mutagenic
- 5 effects of formaldehyde in bone marrow have not been tested in humans.
- 6 Albertini and Kaden (2016) concluded that overall, the available literature on genetic changes following
- 7 formaldehyde exposure did not provide convincing evidence that exogenous exposure, and specifically
- 8 exposure by inhalation, induce mutations as a direct DNA-reactive effect at sites distant from the portal-
- 9 of-entry tissue. This would include proposed mode of actions that involve effecting a stem cell at the
- 10 portal of entry with circulation back to the bone marrow. Such exposures have not been shown to
- induce mutations in the bone marrow or in any other tissues beyond the point of contact. Thus, the
- weight of scientific evidence does not provide biological plausibility of lymphohematopoietic cancers, as
- 13 proposed by EPA (2010) and NTP (2011).

15

### 3.4 Dose-Response Assessment

- 16 Several NRC (2011) peer-review comments were raised regarding the dose-response assessment
- conducted by EPA in the IRIS Draft Assessment (2010). One comment highlighted the need to conduct
- 18 independent analyses of the dose-response models conducted, using the data from the Beane Freeman
- et al. (2009) study to confirm the degree to which the models fit the data appropriately (NRC 2011).
- 20 Using the original data from the key study (Beane Freeman, et al. 2009) and documentation provided in
- 21 the draft IRIS profile, Van Landingham, et al. (2016) attempted to duplicate the reported inhalation unit
- 22 risk (IUR) values for Hodgkin lymphoma and all leukemias and address the NRC Committee's questions
- 23 regarding application of the appropriate dose-response model. Overall, there was difficulty duplicating



| 1  | the IURs reported by EPA (2010), largely due to a lack of critical information provided in the IRIS                    |
|----|------------------------------------------------------------------------------------------------------------------------|
| 2  | documentation. Perhaps most problematic, the first step of the analysis did not determine significant                  |
| 3  | exposure-response relationships between formaldehyde and lymphohematopoietic endpoints for the                         |
| 4  | metric (cumulative exposure) needed in the estimation of an IUR. The authors concluded that the                        |
| 5  | resulting analysis, while it could be mechanically performed, provided no valid or useful insights on the              |
| 6  | risks of formaldehyde exposure. The lack of apparent exposure-response relationships for selected                      |
| 7  | endpoints, raises the question whether quantitative analyses are appropriate for these endpoints, and if               |
| 8  | so, how results are to be interpreted.                                                                                 |
| 9  | The NRC (2011) also noted the need to consider alternative extrapolation models for analyzing the                      |
| 10 | cancer data. In 2013, Starr and Swenberg (2016) proposed a novel "bottom-up" approach for bounding                     |
| 11 | low-dose human cancer risks using formaldehyde as an example. This approach requires information on                    |
| 12 | background risk, background or endogenous exposure and the additional exogenous exposure of                            |
| 13 | interest. The results of this approach provided estimates of risk (<3.9x10 <sup>-6</sup> ) that were more than 14,000- |
| 14 | fold lower than the corresponding EPA (2010) estimate for all leukemias (5.7x10 <sup>-2</sup> ) and considers the      |
| 15 | impact of background endogenous formaldehyde concentrations, which is not considered in the draft                      |
| 16 | EPA (2010) IRIS assessment. In 2016, Starr and Swenberg provided an update to this approach,                           |
| 17 | incorporating new formaldehyde-DNA adduct data, and allowing for uncertainty in two of the                             |
| 18 | parameters (background cancer risk and background endogenous concentrations of formaldehyde).                          |
| 19 | Consideration of the statistical uncertainty in these two parameters resulted in estimates of risk for                 |
| 20 | leukemias that were even smaller than those initially estimated in Starr and Swenberg (2013). The                      |
| 21 | authors concluded that these estimates provide a reality check for the draft EPA IRIS (2010) values. In                |
| 22 | addition, the large discrepancy between results using an approach that relies on molecular dosimetry                   |
| 23 | data (i.e., the bottom up approach) versus one that relies upon uncertain retrospective occupational                   |



| 1 | exposure reconstructions | (i a the approach   | rolled upon in EDA (2010   | \ call into question the | crodibility |
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| 1 | exposure reconstructions | (i.e., the approach | Telled about ill FLY (2010 | 7, can into question the | creaibility |

2 of attributing increases in human mortality from leukemias to occupational exposure to formaldehyde.

3

4

### 3.5 Methods for Evidence Integration

- 5 The NRC (2011) noted that the Draft IRIS Assessment's (2010) approach to weight of evidence should
- 6 include "a single integrative step after assessing all of the individual lines of evidence". Although a
- 7 synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and
- 8 how that evidence was integrated into a final conclusion are not apparent in the draft assessment and
- 9 should be made clear in the final version.
- 10 Since the EPA Draft (2010) and the NRC (2011) peer review, several frameworks have been developed to
- integrate evidence across different lines of scientific inquiry including epidemiology, toxicology and
- mode of action studies (Adami. et al. 2011; Lavelle, et al. 2012; Linkov, et al. 2015; Rhomberg 2015b;
- 13 Rooney, et al. 2014; Woodruff and Sutton, 2014). The EPA has also proposed preliminary approaches
- 14 for integrating evidence in response to the NRC (2011) review of formaldehyde (EPA 2013).
- 15 Rhomberg et al. (2011) applied a hypothesis-based weight of evidence approach to evaluate
- 16 formaldehyde and leukemogenesis, considering how human, animal and mode of action results inform
- one another. In comparing the potential alternative proposals for causality, the authors concluded that
- 18 the evidence for a causal association between formaldehyde exposure and leukemia is not only weak
- but strains biological plausibility (Rhomberg, et al. 2011).
- 20 Nielsen, et al. (2017) also considered the body of formaldehyde research while re-evaluating the WHO
- 21 (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Nielsen, et al. (2017)
- 22 iterated that although formaldehyde is genotoxic and causes DNA adduct formation, it is also



| 1  | clastogenic. Exposure-response relationships from both animal and human data were nonlinear, and                 |
|----|------------------------------------------------------------------------------------------------------------------|
| 2  | relevant genetic polymorphisms had not been identified. Epidemiological studies had inconsistently               |
| 3  | reported associations with nasopharyngeal cancer and leukemia; however, relative risks were not                  |
| 4  | increased below 1 ppm (mean exposures). Because inhaled formaldehyde does not pass beyond the                    |
| 5  | respiratory epithelium, any direct effects are limited to portal-of-entry effects (Nielsen, et al. 2017).        |
| 6  | Other reviews and syntheses of evidence focused on epidemiological studies, and this body of literature          |
| 7  | has been most variably interpreted. In 2014, an independent National Research Council committee was              |
| 8  | charged with peer-reviewing the NTP evaluation of formaldehyde for the 12 <sup>th</sup> revision of the RoC (NRC |
| 9  | 2014b). This NRC committee produced a new definition for "sufficient evidence" of carcinogenicity as             |
| 10 | demonstrated by two or more strong or moderately strong studies with different study designs and                 |
| 11 | populations showing associations between formaldehyde exposure and a specific cancer type. In this               |
| 12 | approach, "strong" epidemiology studies do not refer to the magnitude of the association, but is a               |
| 13 | judgment of study quality and utility made by reviewers who considered chance, bias, and confounding             |
| 14 | as alternative explanations for the observed association and found these were not reasonable                     |
| 15 | explanations. Further, "strong" epidemiology studies comprised large populations with long durations             |
| 16 | of exposure and an adequate follow up period to allow for latency, and had exposure assessments that             |
| 17 | were able to discriminate between "high" and "low" formaldehyde exposure categories. This "strength              |
| 18 | of evidence" approach contrasts with a "weight of evidence approach." Although each epidemiology                 |
| 19 | study was judged as one of three categories (strong, moderately strong, or weak), this approach                  |
| 20 | suggests that 2 or more strong or moderately strong studies with positive results are enough to                  |
| 21 | conclude sufficient evidence of carcinogenicity exists, and discounts epidemiology studies that are              |
| 22 | negative or contradicting, as well as animal studies that are negative or contradicting.                         |
| 23 | Meta-analyses are often used to synthesize findings across many epidemiology studies, identifying                |
| 24 | sources of potential heterogeneity which then can be explored in interpreting the overall evidence. The          |



| 1  | EPA considered meta-analyses conducted by Zhang, et al. 2009; Collins and Lineker, 2004, and Bosetti,   |
|----|---------------------------------------------------------------------------------------------------------|
| 2  | et al. 2008. Since then, two additional meta-analyses were conducted (Bachand, et al. 2010; Schwilk, et |
| 3  | al. 2010). Bachand, et al. (2010) excluded lower-quality studies and reported a meta-RR of 1.05 (95% CI |
| 4  | 0.93 - 1.20) based on 16 cohort studies and a meta-OR of 0.99 (95% CI 0.71 - 1.37) based on 2 case-     |
| 5  | control studies for all leukemia, reported separately due to heterogeneity. Schwilk, et al (2010)       |
| 6  | published a meta-analysis of the epidemiological findings on myeloid leukemia, but limited to the       |
| 7  | highest-exposed sub-group reported in four studies (three cohort and one case-control): RR=2.47; 95%    |
| 8  | CI, 1.42 to 4.27. Checkoway, et al. (2012) conducted a critical review and synthesis of the             |
| 9  | epidemiological evidence and concluded that results from epidemiological studies were not consistent    |
| 10 | and did not show strong results or exposure-response associations. None of these reviews, however,      |
| 11 | included the results from the extended follow up of the NIOSH garment workers study (Meyers, et al.     |
| 12 | 2013) the extended follow up of the UK producers and users (Coggon, et al. 2014) or the extended        |
| 13 | analyses of the NCI cohort (Checkoway, et al. 2015). In addition, meta-analyses and/or critical reviews |
| 14 | of epidemiological literature require further integration with other lines of evidence.                 |

### 4.0 Conclusions

It has been seven years since the release of the EPA (2010) Draft IRIS Toxicological Assessment for Formaldehyde. In peer-reviewing this draft report, an NRC (2011) Committee raised many substantive questions related specifically to the conclusions drawn in the document and the quantitative estimates of potential toxicity. This Committee was limited to the information provided in the assessment, and did not independently conduct a review of the primary literature, but did determine that many of EPA's conclusions were not supported by the information and studies cited in the draft assessment. The committee also identified general methodologic problems with the IRIS Draft Assessment, and provided specific comments related to the evaluation of specific studies and conclusions based on the available



| 4 |          | TL        |                   | 1               | L - 4    | C   -  -   -   -   -   - | exposure and LHM    |
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- 2 largely involved the interpretation of the available evidence at that time and the framework in which it
- 3 was evaluated by EPA (2010). The committee found that EPA's preliminary conclusion that
- 4 formaldehyde causes leukemia, ML or related hematopoietic cancers appeared to be "subjective' in
- 5 nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The
- 6 absence of such a framework was judged by the committee as troublesome, given that the scientific
- 7 evidence on the question was very weak (NRC 2011).
- 8 Since the 2011 NRC Peer Review, significant additional scientific evidence has become available that
- 9 addresses many of the questions raised by the NRC Committee regarding a causal association between
- 10 formaldehyde exposure and LHM. Some of these new studies and analyses were conducted in response
- 11 to their comments, while others reflect ongoing work and updates of studies on this topic. All add to
- 12 the scientific evidence surrounding the potential causal relationship between formaldehyde inhalation
- 13 exposure and LHM, and should be addressed in the critical evaluations and integration of evidence
- 14 presented in an updated IRIS Assessment.
- 15 Also since the NRC Peer Review (2011) of the Draft IRIS Assessment, the EPA has proposed a new IRIS
- 16 process that incorporates many of the general recommendations made by the NRC (2011, 2014a)
- 17 related to methodological issues. This process involves the evaluation and synthesis of evidence within
- separate streams of evidence (human, animal and mechanistic). However, in a critical review of the
- 19 process conducted by a separate NRC (2014a) Committee, while there was improvement in guidelines
- 20 for evaluation and synthesis of evidence within an evidence stream, the NRC (2014a) Committee still
- 21 noted limitations in synthesizing or integrating evidence across streams or categories.
- 22 Nearly all of the recently available evidence from multiple lines of evidence, especially those studies that
- 23 have been focused on addressing comments from the NRC (2011) Committee reviewing the Draft IRIS



| 1  | Assessment, have increased the weight of evidence favouring a conclusion of a lack of a causal                |
|----|---------------------------------------------------------------------------------------------------------------|
| 2  | association between formaldehyde exposure and LHM. The Checkoway et al. (2015) re-analysis using              |
| 3  | the raw data from the Beane Freeman et al. (2009) study was able to address directly several questions        |
| 4  | and comments from the NRC (2011) Committee, as the Draft IRIS Assessment (2010) was highly                    |
| 5  | dependent on its interpretation of this study for drawing both qualitative and quantitative conclusions       |
| 6  | related to formaldehyde leukemogenicity and risk of LHM following inhalation exposure to                      |
| 7  | formaldehyde. The Checkoway et al. (2015) reanalysis provides several results and insights relevant for       |
| 8  | assessing the risk of individual LHM. Not the least of these, the AML specific results provide no support     |
| 9  | for the conclusion that formaldehyde causes AML. Associations seen between formaldehyde exposure              |
| 10 | and Hodgkin lymphoma and CML are inconsistent with other studies and also lack a plausible biological         |
| 11 | mechanism (Checkoway et al. 2015). NTP (2011) also noted that because the evidence for Hodgkin                |
| 12 | lymphoma is mainly limited to the NCI cohort study, a causal association cannot be established. No            |
| 13 | other LHM was associated with either cumulative or peak formaldehyde exposure. These results of the           |
| 14 | fuller analysis of the data from Beane Freeman et al. (2009) are consistent with recent epidemiological       |
| 15 | studies (Meyers, et al. 2013; Saberi Hosnijeh, et al. 2013; Talibov, et al. 2014) which report no significant |
| 16 | increase in LHM, specifically AML, among cohorts of workers exposed to formaldehyde.                          |
| 17 | The available animal evidence did not support a causal association between formaldehyde exposure and          |
| 18 | LHM at the time the EPA Draft (2010) was released. Since that time, two additional studies have been          |
| 19 | conducted by the NTP (Morgan 2017) using two sensitive assays in mice genetically predisposed to              |
| 20 | develop cancer following short-term exposure to a chemical. These studies provided no evidence of             |
| 21 | changes in endpoints related to LHM or the presence of any LHM following exposure to high                     |
| 22 | concentrations (15 ppm) of formaldehyde.                                                                      |
| 23 | Studies conducted to evaluate potential mechanisms associated with formaldehyde exposure and LHM              |
| 24 | have demonstrated a lack of evidence for exogenous formaldehyde to move beyond the portal of entry.           |



| 1  | Multiple studies conducted in multiple species using a highly sensitive technique (Edrissi, et al. 2013; Lu, |
|----|--------------------------------------------------------------------------------------------------------------|
| 2  | et al. 2011; Moeller, et al. 2011; Yu, et al. 2015) have demonstrated that while endogenous                  |
| 3  | formaldehyde is present in all tissues, exogenous formaldehyde following inhalation exposure is not          |
| 4  | transported systemically. While some mechanisms for the development of LHM following inhalation              |
| 5  | exposure to formaldehyde have been hypothesized (EPA 2010; Zhang, et al. 2009, 2010), there is no            |
| 6  | evidence to support these proposed mechanisms and the NRC (2011) Committee noted that:                       |
| 7  | "Although EPA postulated that formaldehyde could reach the bone marrow either as                             |
| 8  | methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies                   |
| 9  | described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at               |
| 10 | concentrations below those which overwhelm metabolism according to sensitive and selective                   |
| 11 | analytic methods that can differentiate endogenous from exogenous exposures."                                |
| 12 | The more recent research all but confirms this. Several modes of action have been proposed, relying          |
|    |                                                                                                              |
| 13 | primarily on data reported by Zhang et al. (2010) as well as subsequent evaluations of the same              |
| 14 | population of Chinese workers (Bassig, et al. 2016; Lan, et al. 2015; Seow et al. 2015). These include a     |
| 15 | mode of action in which risk of ML is increased due to immune suppression resulting from formaldehyde        |
| 16 | exposure (Bassig et al. 2016; Seow et al. 2015). The speculated modes of action, however, assume             |
| 17 | systemic delivery of formaldehyde except one, which is a hypothesized mode of action in which                |
| 18 | hematopoietic cells in the nasal epithelium that are impacted by exposure to formaldehyde return to          |
| 19 | the bone marrow. The NRC (2011) Committee considered this proposed mode of action and concluded              |
| 20 | that:                                                                                                        |
| 21 | "As a result, EPA could only speculate that circulating hematopoietic stem cells that percolate              |
| 22 | through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for                |



| <i>a</i> |                 |                          |                        | lymphohemotopoietic cancers.    |
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- 2 Experimental evidence of [this] mechanism is lacking."
- 3 This currently leaves no acceptable proposed mode of action for the development of LHM following
- 4 inhalation exposure to formaldehyde that can be scientifically substantiated.
- 5 The available toxicokinetic data also do not support the transport of inhaled formaldehyde from the
- 6 portal of entry. The studies by Swenberg and colleagues unequivocally demonstrate that exogenous
- 7 formaldehyde exposure does not increase formaldehyde concentrations measured in any internal
- 8 tissues over those in unexposed animals, i.e., endogenously produced formaldehyde is the predominant
- 9 if not only source of internal formaldehyde (Edrissi, et al. 2013; Lu, et al. 2010, 2011; Moeller, et al.
- 10 2011; Swenberg, et al. 2011; Yu 2015).
- 11 The biological plausibility of a mode of action for the development of LHM following inhalation exposure
- 12 to formaldehyde has relied heavily upon the incomplete results from the Zhang et al. (2010) study in
- which the authors report differences between groups of formaldehyde exposed and unexposed groups
- in the frequency of monosomy 7 (loss of chromosome) and trisomy 8 (gain of chromosome), based on
- 15 metaphase spreads prepared from culture of CFU-GM colony cells. However, reanalysis of the
- 16 underlying raw data in two studies (Gentry, et al. 2013; Mundt, et al. 2017) have identified
- 17 methodological problems with this study that challenge these conclusions, as well as demonstrate a lack
- 18 of association between level of formaldehyde exposure and the observed aneuploidy (or any of the
- 19 haematological measures).
- 20 Overall, the quality and amount of evidence relevant to the understanding of a potential causal
- 21 relationship between formaldehyde inhalation exposure and risk of LHM has increased substantially
- 22 since the completion of the EPA (2010) Draft IRIS Assessment and release of the 2011 NRC Peer Review
- 23 of the Draft Assessment. New evidence has been published in each of the major streams of evidence



| 1  | (i.e., human, animal and mechanistic) that consistently indicates a lack of a causal association between     |
|----|--------------------------------------------------------------------------------------------------------------|
| 2  | formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the            |
| 3  | NRC (2011) criticisms surrounding the evaluation of a combination of cancer types, as well as increased      |
| 4  | our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical      |
| 5  | in attempting to understand the potential hazards or risks from formaldehyde exposure. Regardless of         |
| 6  | which of the several similar approaches to integrating the available evidence between formaldehyde           |
| 7  | inhalation exposure and the potential for leukemia risk, there is at most only limited suggestive positive   |
| 8  | evidence, in contrast with the bulk of evidence suggesting no such association. Therefore, a conclusion      |
| 9  | of causation is not justified scientifically. The scientific landscape into which EPA will release its long- |
| 10 | anticipated revised IRIS Toxicological Review of Formaldehyde – Inhalation Assessment is very different      |
| 11 | from that of the 2010 Draft IRIS Assessment, both in terms of improved methodological approaches and         |
| 12 | the available epidemiological, toxicological and mechanistic evidence. Given formaldehyde's                  |
| 13 | commercial importance, ubiquity in the environment and endogenous production, accurate                       |
| 14 | determination of whether exposure to formaldehyde from occupational, residential and consumer                |
| 15 | products causes leukemia or any type of human neoplasm is critical.                                          |

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Table 1. Summary of major formaldehyde carcinogenicity classifications and noted scientific basis

| Year              | Agency                                                           | Carcinogenicity<br>Classification          | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------|------------------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                   |                                                                  |                                            | Epidemiological evidence. Not discussed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 1981              | NTP<br>(2 <sup>nd</sup> Report on<br>Carcinogens,<br>1981)       | Anticipated to be a human carcinogen       | Toxicological evidence. One study cited (Swenberg et al. 1980).  "While a full evaluation of the carcinogenicity of formaldehyde vapor must await completion of studies at the Chemical Industry Institute of Toxicology, evidence presented to date demonstrates that inhalation of formaldehyde results in a high incidence of nasal cancers in rats (Swenberg et al. 1980)."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                   | IARC                                                             | Probably                                   | Epidemiological evidence. Inadequate (6 epidemiology studies)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 1981 <sup>a</sup> | (Monograph<br>Volume 29, 1982<br>and Monograph<br>Suppl 4, 1982) | carcinogenic to<br>humans<br>(Group 2B)    | Toxicological evidence. Sufficient, formaldehyde is carcinogenic to rat, causes nasal cancers.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                   |                                                                  | Anticipated to be                          | Epidemiological evidence. Inadequate (cites IARC, 1982, Suppl 4, IARC, 1982, Volume 29)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 1982              | INID                                                             |                                            | <b>Toxicological evidence.</b> Sufficient, formaldehyde is carcinogenic to two strains of rats. Nasal cancers. One test in mice did not produce statistically significant results. Other studies in animals (mice and hamsters by inhalation exposure) were considered inadequate for evaluation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1987 <sup>b</sup> | IARC<br>(Monograph Suppl<br>7, 1987)                             | Probably carcinogenic to humans (Group 2A) | Epidemiological evidence. Limited Reported epidemiological evidence is strongest for nasal and nasopharyngeal cancer, noted limitations with small numbers of exposed cases and inconsistent reports.  Leukemia: "Excess mortality from leukemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excess for these cancers among professionals is due to conditions other than formaldehyde. The slight excesses of cancer among professionals noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level, or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies."  Toxicological evidence. Sufficient No changes in information reported from IARC, Suppl 4, 1982  Supporting data.  "In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings (IARC, Suppl 6, 1987)." |



| Year              | Agency                               | Carcinogenicity<br>Classification                   | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------|--------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1991              | EPA (EPA, 1991)                      | Probable human<br>carcinogen<br>(Group B1)          | "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products." (p.7)  Leukemia: "Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated." (p. 8)  Toxicological evidence. Sufficient, nasal squamous cell carcinomas  Increased incidence of nasal squamous cell carcinomas observed in rats and mice in long-term inhalation studies.  Supporting data.  "The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde." (p. 7)                                                                                                                                                                                                                                                                                                                                                                                                        |
| 1994 <sup>c</sup> | IARC (Monographs<br>Volume 62, 1995) | Probably<br>carcinogenic to<br>humans<br>(Group 2A) | Epidemiological evidence. Limited  Lack of consistency between cohort and case-control studies of cancers of the nasal cavities and paranasal sinuses.  Leukemia: "The studies of industrial cohorts also showed low or no risk for lymphatic or haematopoietic cancers; however, the cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by a consistent lack of excess risk for brain cancer in the studies of industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists." (p.334)  Toxicological evidence. Sufficient (nasal squamous cell carcinomas)  Squamous cell carcinomas of nasal cavities, at highest exposure. No evidence of carcinogenicity in hamsters. Mice showed no effect or were inadequate for evaluation.  Supporting data. Genotoxic in variety of experimental systems in vivo. Induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, gene mutation in human and rodent cells in vitro. |



| Year              | Agency                                       | Carcinogenicity<br>Classification      | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------|----------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2004 <sup>d</sup> | IARC (Monographs<br>Volume 88, 2006)         | Carcinogenic to<br>humans (Group<br>1) | Leukemia: "There is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers." (p.276)  Toxicological evidence. Sufficient (nasal squamous cell carcinoma)  Supporting data. Mechanism for inducing myeloid leukema is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells.  "The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukaemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans." (p. 280)                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2009 <sup>e</sup> | IARC<br>(Monographs<br>Volume 100F,<br>2012) | Carcinogenic to humans (Group 1)       | Epidemiological evidence. Formaldehyde causes cancer of the nasopharynx and leukaemia.  "The Working Group was not in full agreement on the evaluation of formaldehyde causing leukaemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited." (p. 430)  Toxicological evidence.  "Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427)  "Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p.428)  Inconsistent genotoxic effects in blood lymphocytes from animals exposed to formaldehyde via inhalation.  Supporting data. "Particularly relevant to the discussions regarding sufficient evidence was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukeaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological prescursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430)  "Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the mechanisms is the most important." (p. 430) |



| Year | Agency                                               | Carcinogenicity<br>Classification | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------|------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |                                                      | Classification                    | Epidemiological evidence. Sufficient                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 2010 | EPA<br>(Draft IRIS<br>Toxicological<br>Review, 2010) | Carcinogenic to<br>humans         | "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (page 6-46).  For all LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts (embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (page 4-180).  For all leukemias as a group: "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group." (page 4-182)  Toxicological evidence. Limited evidence to support conclusion that formaldehyde exposure causes leukemia. Four studies evaluated the leukemic potential of formaldehyde.  "Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after chronic inhalation exposures (Sellakumar et al., 1985)." (p.6-21) |
|      |                                                      |                                   | Supporting data.  "Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been coumented in formaldehyde exposed workers, including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells." (p.6-22)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 2012 | NTP<br>(12 <sup>th</sup> RoC, 2013)                  | Known to be a human carcinogen    | "Epidemiological evidence. Causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia  "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia." (p. 195)  Toxicological evidence. No specific evidence cited regarding leukemia beyond the following: "Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |



| Year | Agency                   | Carcinogenicity<br>Classification                  | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------|--------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |                          | Classification                                     | after long-term exposure of adults; however, it is unclear whether these turmos were exposure-related, because of limitations in the reporting of these tumors (Soffritti et al., 2002)." (p. 198)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|      |                          |                                                    | Supporting data.  "Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al. 2010a). Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. The endogenous concentration in the blood of humans, monkeys, and rats is about 2 to 3 μg/g, and the concentration does not increase after inhalation of formaldehyde from exogenous sources (Heck et al. 1985, Casanova et al. 1988, Heck and Casanova et al. 2004). Moreover, N2-hydroxymethyldG–DNA adducts have not been detected at distal sites in rats (such as the bone marrow, white blood cells, lung, spleen, liver, or thymus) (Lu et al. 2010). For these reasons, the plausibility of formaldehyde's causing cancer at distal sites, such as myeloid leukemia, has been questioned (Golden et al. 2006, Pyatt et al. 2008).  However, systemic effects have been observed after inhalation or oral exposure, and although the mechanisms by which formaldehyde causes myeloid leukemia in humans are not known, a number of plausible mechanisms have been advanced. These include (1) theoretical mechanisms for the distribution of formaldehyde to distal sites and (2) proposed mechanisms of leukemogenesis that do not require formaldehyde to reach the bone marrow. In addition, there is some evidence that formaldehyde |
|      |                          |                                                    | causes adverse haematological effects in humans." (p. 199)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2012 | RAC<br>(RAC, ECHA, 2012) | Carc. 1B - H50 <sup>f</sup><br>May cause<br>cancer | "In conclusion, while some studies have found increased rates of leukaemia, the epidemiology data do not show consistent findings across studies for leukaemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukaemia rates among embalmers, pathologist and anatomists, but not among industrial workers, suggests the possibility of confounding factors that bear investigation. Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukaemia." (p.41)  Toxicological evidence. "No indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumours in inhalation study of rats and mice (Kerns et al. 1983)." (p.22)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|      |                          |                                                    | <b>Supporting data</b> . "Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found at values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |



| Year | Agency                                                                              | Carcinogenicity                                                                                | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |                                                                                     | Classification                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|      |                                                                                     |                                                                                                | These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the orogastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the port of entry." (p.44)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 2016 | Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL, 2016) | Carcinogen<br>Group C<br>(genotoxic<br>carcinogen with<br>a mode-of-action<br>based threshold) | Epidemiological evidence.  "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45)  Toxicological Evidence. "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49)  Supporting Data. "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49) |

<sup>&</sup>lt;sup>a</sup>IARC Working Group met February 1981. IARC Preamble (1982): "For many of the chemicals evaluated in the first 29 volumes of the /ARC Monographs for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer."



<sup>&</sup>lt;sup>b</sup>IARC Working Group met March 1987.

<sup>&</sup>lt;sup>c</sup>IARC Working Group met October 1994; monograph published 1995.

dIARC Working Group met June 2004; monograph published 2006.

<sup>&</sup>lt;sup>e</sup>IARC Working Group met October 2009; monograph published 2012.

<sup>&</sup>lt;sup>f</sup>EU harmonized classification and labelling.

Table 2: Summary of NAS (2011) Comments or Identified Data Gaps and New Formaldehyde Science by Lines of Inquiry

| NAS (2011) Comment / Identified Data Gap                                                                                                                                                                                       | New Formaldehyde Science                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A. Epidemiolo                                                                                                                                                                                                                  | gical Evidence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (NAS, p. 113)                                   | New analyses of the NCI formaldehyde workers cohort specifically for AML are reported. Results do not support the hypothesis that formaldehyde causes AML.  Checkoway et al. (2015)  Associations seen between formaldehyde exposure and Hodgkin lymphoma and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. Checkoway et al. (2015)                                                                                                                                                    |
| Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. (NAS, p. 113) | A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoetic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation.  Checkoway et al. (2012)                                                                                                                                                                                                                              |
| Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (NAS, p. 112-113)                                                    | Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure, and few deaths occurred within 20 or more years of last peak exposure. Suggestive associations with peak exposure were observed for chronic myeloid leukemia, based on very small numbers. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (ptrend= 0.05) and peak (ptrend= 0.003) exposures. However, no other lymphohematopoietic malignancy was associated with either cumulative or peak exposure.  Checkoway et al. (2015) |
| The selection and use of the NCI cohort (Beane-Freeman et al. 2009) should be further justified. (NAS, p. 112)                                                                                                                 | Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941-2012. Results provide no support for an increased hazard of myeloid leukemia from formaldehyde exposure.  Coggon et al. (2014)                                                                                                                                                                                                                                                                                            |



| NAS (2011) Comment / Identified Data Gap                                                                                                                                                                                                                                                                                                        | New Formaldehyde Science                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                 | Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results demonstrated limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases.  Meyers et al. (2013)                                                                                                                                                                                                                                                                                                                                                                          |
| B. Toxicologi                                                                                                                                                                                                                                                                                                                                   | ical Evidence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (NAS, p. 110) | No cases of leukemia or lymphohematopoietic neoplasia were seen. FA inhalation did not cause leukemia in genetically predisposed C3B6.129F1- Trp53tm1Brd mice. Morgan et al. (2014)                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                 | FA inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. <i>Morgan et al. (2015)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| C. Mode of Ac                                                                                                                                                                                                                                                                                                                                   | tion Evidence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (NAS, p. 58)                                                                                                                                                                                                    | Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations.  Schroeter et al. (2014)                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                 | With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. <i>Yu et al. (2015)</i> |



| NAS (2011) Comment / Identified Data Gap                                                                                                                                 | New Formaldehyde Science                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reconcile divergent statements regarding systemic delivery of formaldehyde (p.59); direct evidence of systemic delivery of formaldehyde is generally lacking. (NAS, p.5) | Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. Also, new evidence suggests that endogenous formaldehyde in bone marrow is toxic and carcinogenic, and may cause leukemia (but not exogenous formaldehyde).  Lai et al. (2016)  Gao et al. (2016)  Yu et al. (2015)  Edrissi et al. (2011)  Lu et al. (2011)                                                                             |
| Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (NAS, p. 5)                                            | Critical review of the genotoxicity literature found no convincing evidence that exogenous exposures to FA alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically not in the bone marrow.  Review of the existing studies of hematotoxicity, likewise, failed to demonstrate myelotoxicity in any species— a probable prerequisite for leukemogenesis.  Albertini and Kaden (2016)                                                                                                                                       |
|                                                                                                                                                                          | Reanalysis of selected raw data from the Zhang et al. (2010) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect in vivo events, the reanalysis of the results provided by Zhang et al. (2010) raise sufficient questions that limit the use of Zhang et al. (2010) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. <i>Gentry et al. (2013)</i> |



| NAS (2011) Comment / Identified Data Gap                                                                                                                                                                   | New Formaldehyde Science                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
|                                                                                                                                                                                                            | Additional analyses were performed on the study data obtained from the original study (Zhang et al. 2010) including individual average formaldehyde exposure concentration measurements performed for each exposed worker. The objective was to evaluate hematological parameters and aneuploidy in relation to quantitative exposure measures of formaldehyde. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Furthermore, among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk.  Mundt et al. (2017) |  |  |  |
| D. Dose-Response Assessment                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. (NAS, p. 14)                                                              | The documentation of the methods applied in the USEPA (2010) IRIS document lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the Beane Freeman et al. (2010). This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints.  Van Landingham et al. (2016)                                                                                                                                                                                                                                                                                              |  |  |  |
| BBDR models developed by Conolly and co-workers should be used. (p.58) These models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. (NAS, p.57) | Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations.  Clewell et al. (in preparation)                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |  |



| NAS (2011) Comment / Identified Data Gap                                                                                                                                                                                                                                                                                                                                                                                  | New Formaldehyde Science                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (NAS, $p.14$ )                                                                                                                                                                                                                                                                                                          | Results of the "Bottom-up" approach indicate that recent top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins.  Starr and Swenberg (2013)                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                           | Updated "Bottom-Up" risk estimates heighten the marked contrasts that are present between the previous estimates and the corresponding USEPA estimates, with the larger difference for leukemia being due primarily to the significantly improved detection limit for the analytical method used in quantitating DNA adduct numbers.  Starr and Swenberg (2016)                                                                                                                                                                                                                                                                                      |  |  |
| E. Methods for Evidence Integration                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |
| EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (NAS, p. 113) | A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode-of-action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. <i>Rhomberg et al.</i> (2011) |  |  |



## Highlights

- A 2011 NRC report challenged leukemia causation in IRIS Draft Formaldehyde Review
- Studies published since IRIS Draft provide new evidence for evaluating formaldehyde
- Integration of evidence does not support formaldehyde as a cause of leukemia
- Valid hazard classification of formaldehyde has significant regulatory implications



### Message

From: Thayer, Kris [thayer.kris@epa.gov]

**Sent**: 12/4/2017 3:03:39 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Bussard, David

[Bussard.David@epa.gov]; Bateson, Thomas [Bateson.Thomas@epa.gov]

CC: Bahadori, Tina [Bahadori.Tina@epa.gov]

Subject: Fwd: Follow-up

Attachments: Mundt et al 2017 - Six Year aftr NRC Review.pdf; ATT00001.htm

FYI

Sent from my iPhone

Begin forwarded message:

From: "Orme-Zavaleta, Jennifer" < Orme-Zavaleta.Jennifer@epa.gov>

Date: December 4, 2017 at 8:49:33 AM EST

To: "Bahadori, Tina" < Bahadori. Tina@epa.gov >, "Thayer, Kris" < thayer.kris@epa.gov >

Subject: FW: Follow-up

To start your week...

Jennifer Orme-Zavaleta, PhD
Principal Deputy Assistant Administrator for Science
USEPA Office of Research and Development

Ex. 6 - Personal Privacy

orme-zavaleta.jennifer@epa.gov

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta.

Thank you for your initial response to my November 21<sup>st</sup> letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22<sup>nd</sup> to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]



Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulator y implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA<sup>1</sup>, Gentry PR<sup>2</sup>, Dell LD<sup>2</sup>, Rodricks JV<sup>2</sup>, Boffetta P<sup>3</sup>. Author information
Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRISreview and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

### **KEYWORDS:**

| Epidemiology; | Evidence integration; | Hazard evaluation; | Mechanistic studie | es; Regulatory | science; |
|---------------|-----------------------|--------------------|--------------------|----------------|----------|
| Toxicology    |                       |                    |                    |                |          |

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
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### Message

 From:
 Soto, Vicki [Soto.Vicki@epa.gov]

 Sent:
 12/18/2017 10:17:38 PM

To: Jones, Samantha [Jones.Samantha@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]; Lavoie, Emma

[Lavoie.Emma@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]; Avery, James [Avery.James@epa.gov]; Shams,

Dahnish [Shams.Dahnish@epa.gov]

**Subject**: RE: updates to MYA chemicals - path forward

They were on the 2012 agenda

From: Jones, Samantha

Sent: Monday, December 18, 2017 5:09 PM

To: Soto, Vicki <Soto.Vicki@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Lavoie, Emma

<Lavoie.Emma@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Avery, James <Avery.James@epa.gov>; Shams,

Dahnish <Shams.Dahnish@epa.gov>

Subject: RE: updates to MYA chemicals - path forward

Can you remind me why the chemicals not categorized as Table 1 or MYA are on this list? Are they the rest of the chemicals from the 2012 agenda? A subset of those?

----Original Appointment----

From: Soto, Vicki

Sent: Thursday, November 16, 2017 8:49 AM

To: Soto, Vicki; Bahadori, Tina; Lavoie, Emma; D'Amico, Louis; Jones, Samantha; Avery, James; Shams, Dahnish

Subject: updates to MYA chemicals - path forward

When: Tuesday, December 19, 2017 4:00 PM-5:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: DCRoomRRB71214-NCEADir

Further discussion on updating the IRIS agenda and scheduling current work. Tina − I hope this is the right conference room □

There is a little bit of time conflict – I hope this time works for everyone.







### Message

From: Soto, Vicki [Soto.Vicki@epa.gov]

**Sent**: 12/19/2017 9:00:11 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; D'Amico, Louis

[DAmico.Louis@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Avery,

James [Avery.James@epa.gov]; Shams, Dahnish [Shams.Dahnish@epa.gov]

**Subject**: RE: updates to MYA chemicals - path forward

Hi – I don't know if we need to have this meeting, it seems like the one we had two weeks ago is sufficient.

I will cancel this – let me know if I need to reschedule.

Vicki

----Original Appointment----

From: Soto, Vicki

Sent: Thursday, November 16, 2017 8:49 AM

To: Soto, Vicki; Bahadori, Tina; Lavoie, Emma; D'Amico, Louis; Jones, Samantha; Thayer, Kris; Avery, James; Shams,

Dahnish

Subject: updates to MYA chemicals - path forward

When: Tuesday, December 19, 2017 4:00 PM-5:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: DCRoomRRB71214-NCEADir

Further discussion on updating the IRIS agenda and scheduling current work. Tina − I hope this is the right conference room 

Output

Description:

There is a little bit of time conflict – I hope this time works for everyone.





### Message

From: Gwinn, Maureen [gwinn.maureen@epa.gov]

**Sent**: 1/30/2018 5:51:56 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]

Subject: Re: PS

I just heard thanks

Maureen R Gwinn PhD DABT
Office of Research and Development
US Environmental Protection Agency

(202)564-4621 office

Ex. 6 - Personal Privacy

On Jan 30, 2018, at 12:45 PM, Bahadori, Tina < Bahadori, Tina@epa.gov> wrote:

## Ex. 6 - Personal Privacy

From: Gwinn, Maureen

**Sent:** Tuesday, January 30, 2018 12:42 PM **To:** Bahadori, Tina <a href="mailto:8ahadori.Tina@epa.gov">8ahadori.Tina@epa.gov</a>

Subject: Re: Pruitt hearing

I did lose video briefly but I don't think it came up

Maureen R Gwinn PhD DABT
Office of Research and Development
US Environmental Protection Agency

(202)564-4621 office

Ex. 6 - Personal Privacy

On Jan 30, 2018, at 12:35 PM, Bahadori, Tina <Bahadori, Tina@epa.gov> wrote:

JOZ thought there would be an IRIS question....thanks for being our eyes and ears.

T>

From: Gwinn, Maureen

**Sent:** Tuesday, January 30, 2018 12:35 PM **To:** Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>

Subject: Re: Pruitt hearing

A lot on wotus too

Maureen R Gwinn PhD DABT Office of Research and Development US Environmental Protection Agency

(202)564-4621 office

Ex. 6 - Personal Privacy



### On Jan 30, 2018, at 12:28 PM, Bahadori, Tina < Bahadori, Tina@epa.gov > wrote:

Thanks! Was he asked about IRIS, in general??

From: Gwinn, Maureen

**Sent:** Tuesday, January 30, 2018 12:21 PM

To: Jones, Samantha < Jones. Samantha@epa.gov >; D'Amico, Louis

<DAmico.Louis@epa.gov>

Cc: Bahadori, Tina <<u>Bahadori</u>, Tina@epa.gov>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>> **Subject:** Pruitt hearing

In case you are not watching - just a heads-up that the formaldehyde assessment was brought up by Senator Ed Markey at 12:15 or so in the hearing. He has asked for a response on the status within 10 days.

I know we'll get QFRs in full, but just wanted to pass this one along because 10 days is a short time frame.

Maureen R. Gwinn, PhD DABT ATS
Senior Science Advisor
National Center for Computational Toxicology
Office of Research and Development
1200 Pennsylvania Ave NW
MC 8101R
Washington, DC 20460

t(202)564-4621 f(202)565-2430

M Ex. 6 - Personal Privacy



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 1/6/2018 10:48:01 PM

To: Mantus, Ellen [EMantus@nas.edu]; Fryberger, Teresa [TFryberger@nas.edu]

**Subject**: IRIS requirements in the FY 17 Appropriations Bill

Hi, this is the FY17 language we were alluding to on Friday.

Tina

The explanatory statement says: Integrated Risk Information System (IRIS). - The Committees are aware of efforts to implement

the 2011 National Academy of Science's (NAS) Chapter 7 and 2014 NAS report recommendations for the IRIS program, including six specified recommendations. These recommendations include objective evaluation of the strengths and weaknesses of critical studies, the need for weight of evidence evaluation and integration, and clearer rationale for selecting studies to calculate toxicity values. Additionally, the NAS identified specified recommendations and considerations when evaluating the hazards of formaldehyde. The Committees believe that EPA should contract with the NAS to conduct the peer review of the revised draft IRIS assessment of formaldehyde, should it be released in fiscal year 2017, to verify the recommendations from the previous NAS report of 2011 have been fully resolved scientifically.

The House report says: Integrated Risk Information System (IRIS) and other assessments.—

At least six critical recommendations from the National Academy of Sciences (NAS) have yet to be implemented including objective evaluation of the strengths and weaknesses of critical studies, the need for weight of evidence evaluation and integration, and clearer rationale for selecting studies to calculate toxicity values. Additionally, the NAS identified specific concerns that need to be addressed when evaluating the hazards of formaldehyde. The Committee believes it is essential for the NAS to peer review the revised draft assessment of formaldehyde to verify whether EPA has addressed all previous recommendations. In addition, for all draft or final EPA risk assessments issued in fiscal year 2017, the Committee directs the Agency to provide clear

fiscal year 2017, the Committee directs the Agency to provide clear criteria for judging the quality of all key studies and to provide a description of how all evidence will be integrated, based on its

strengths and weaknesses, in advance of releasing any future draft assessments. When evaluating the potential carcinogenic effects of substances, the Agency shall also present non-linear modeling approaches.

Consistent with EPA's Risk Characterization Handbook

(EPA, 2002), draft and final hazard and exposure assessments, produced

by EPA offices, should also include the distribution of estimated

hazards, exposures, or risks, including central tendency values.

The Senate report says: Integrated Risk Information System.—The Committee is aware of efforts by the Agency to implement the 2011 National Academy of Science's [NAS] Chapter 7 and 2014 NAS report recommendations for the Integrated Risk Information System [IRIS] but remains concerned that the recommendations have not been fully implemented.

In published appendices that accompany final IRIS assessments, EPA has detailed some of the Agency's deficiencies in meeting the NAS high-priority reforms. The Committee directs the Agency to convene an interagency working group to be Co-Chaired with the Office of Information and Regulatory Affairs and to include relevant executive branch stakeholders to review compliance with the NAS recommendations in IRIS assessments issued since the 2014 NAS report. The working group shall focus specifically on transition from the use of single point estimates of hazard and exposure



to presenting more complete information on the distribution of estimated hazards, exposures, and/or risks, including central tendency values; on processes for evaluating study quality, relevance, and risk of bias; the use of a transparent and reproducible weight-of evidence process for applying scientific findings; the selection of an adverse outcome; and the use of default linear low-dose extrapolation and other default modeling approaches to hazard determinations. The Committee directs the Agency to issue a report to the Committees of Appropriations of the House and Senate on the findings of the working group and the implementation plans of its findings within 180 days of enactment of this act. The working group report shall also include a timetable for EPA's full implementation of the NAS recommendations for all IRIS assessments issued since the 2014 NAS report.





### UNITED STATES ENVIRONMENTAL PROTECTION AGENCY National Center for Environmental Assessment Washington, DC 20460

OFFICE OF RESEARCH AND DEVELOPMENT

October 06, 2017

Kimberly Wise White, Ph.D.
Senior Director
American Chemistry Council
Chemical Products and Technology Division
On Behalf of the ACC Formaldehyde Panel
700 Second St., NE
Washington, DC 20002

Dear Dr. Wise White,

Thank you for your letter of September 13, 2017 reiterating the American Chemistry Council (ACC) Formaldehyde Panel's interest in the EPA's formaldehyde IRIS assessment. I forwarded a copy of your letter and the accompanying National Toxicology Program (NTP) report to the assessment team. The assessment team is aware of this report and will be including consideration of its findings in the public comment draft of the formaldehyde assessment.

I would like to reassure you and the Panel again that we are very aware of the importance of this assessment and are mindful of your concerns. This is why we hope to complete the draft of this assessment as expeditiously as possible and make it available for public comment and peer review by the National Academy of Sciences (NAS). We are also aware that the Panel has been committed to conducting research to address the recommendations of the NAS and engaging scientists on approaches to integrate the scientific evidence for formaldehyde. As you indicated, EPA scientists will participate in the ACC-sponsored October workshop.

In your letter, you also raised a number of questions about the draft assessment which we addressed separately below. But truthfully, the only way to demonstrate our commitment to a scientifically robust and transparent formaldehyde assessment is to present the document for public comment and rigorous peer review by the NAS.



Again, thank you for your letter. Should you have further questions, you may contact me by phone (703-347-8600), or email (bahadori.tina@epa.gov).

Sincerely,

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment National Program Director, Human Health Risk Assessment U.S. EPA, Office of Research and Development

CC: Robert Kavlock Richard Yamada Kris Thayer Dan Morgan



### Responses to ACC Questions on the IRIS Toxicological Review of Formaldehyde (October 2017)

1. How is EPA considering new scientific information, like the NTP study, for incorporation into the weight of evidence for the formaldehyde IRIS assessment?

EPA is carefully reviewing and considering new, peer-reviewed science as it becomes available, for inclusion in the revised draft formaldehyde assessment. We are fully incorporating the NTP study into the current draft assessment.

2. When did EPA last conduct a search of the formaldehyde literature for science to incorporate into the IRIS assessment and how frequently does EPA monitor the formaldehyde literature to identify potential studies that should be incorporated into the assessment?

The last formal literature search was completed in October, 2016, and the next formal literature search is currently underway. In addition, the assessment managers and team of scientists working on the assessment continually monitor the scientific literature for awareness and consideration of the latest available research. Our partners and stakeholders who have great interest in this assessment have remained vigilant in ensuring that all pertinent studies are brought to our attention and confirming that our formal and informal searches are complete. The NTP study is just one example of that very situation, where a document released after the last formal literature search has already been incorporated into the draft assessment, as appropriate.

3. What guidance documents or procedures will EPA utilize to evaluate study quality for studies relied upon to reach conclusions in the formaldehyde IRIS assessment? Please provide specific references if available.

EPA will be using Agency risk assessment guidelines as a framework for evaluating study quality and to reach conclusions in the draft formaldehyde assessment. Public guidance documents can easily be accessed at <a href="https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance">https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance</a>. In addition, as you know, EPA has been incorporating principles of systematic review into the assessment development process, in response to the recommendations from the 2011 and 2014 NAS reports. The draft assessment which we hope to share with the public soon will transparently explain the procedures utilized in development of the assessment.

4. When will EPA release a weight of evidence framework illustrating how various data streams (i.e. mechanistic, toxicology and epidemiology studies) are evaluated for quality and then integrated to reach conclusions about formaldehyde?

EPA is using existing Agency guidance to weigh, synthesize, and integrate evidence to evaluate formaldehyde toxicity. The criteria used for identifying studies, evaluating quality, and integrating evidence streams, will be clearly and transparently described in the formaldehyde assessment, as was recommended by the NAS.



5. How has EPA addressed all the 2011 NAS recommendations for formaldehyde?

EPA has addressed all the 2011 NAS recommendations for formaldehyde in the revised draft assessment. A section in the appendix will clearly describe how the Agency addressed the recommendations.

6. How will EPA seek public input and peer review on the formaldehyde IRIS assessment and what types of public meetings or workshops will be held to receive input?

The revised draft formaldehyde assessment EPA will follow the established IRIS process. Following agency and interagency review, the draft assessment will be released for public comment, and an accompanying public science meeting. Following the public comment draft, EPA will make any necessary revisions, and a peer review draft will be released for independent peer review by the NAS. The NAS peer review will also include an opportunity for public comment.



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 12/14/2017 11:05:29 AM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

CC: Glenn, Barbara [Glenn.Barbara@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]

**Subject**: RE: Formaldehyde IRIS assessment

This will be relevant to our update conversation this afternoon.

Τ.

From: Kraft, Andrew

Sent: Wednesday, December 13, 2017 3:44 PM

**To:** Bahadori, Tina <Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov> **Cc:** Glenn, Barbara <Glenn.Barbara@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>

Subject: FW: Formaldehyde IRIS assessment

FYI, Tina and Kris, i

#### Ex. 5 - Deliberative Process

### Ex. 5 - Deliberative Process

From: Deveau, Michelle (HC/SC) [mailto:michelle.deveau@canada.ca]

**Sent:** Thursday, September 28, 2017 4:10 PM **To:** Kraft, Andrew < <u>Kraft.Andrew@epa.gov</u>> **Subject:** Formaldehyde IRIS assessment

Hi Andrew,

We met briefly at your poster session at SOT 2016 (in New Orleans). I'm with the indoor air group at Health Canada, and we're thinking of reassessing our Residential Indoor Air Quality Guideline for formaldehyde. I was wondering if you'd be able to provide any information to me on your expected timelines for your IRIS assessment on formaldehyde. Are you still moving forward with updating your assessment? And do you have any approximate timelines on when you hope to have a draft published?

Your assessment is something that we would potentially be considering quite a bit if we did decide to reassess our guideline, so it would be very helpful if you are able to provide any possible information for us.

Thanks in advance for any information you can give me, Michelle

Michelle Deveau, MSc(A), ROH

Senior Scientific Evaluator, Indoor Air Contaminants Assessment Section, Healthy Environments and Consumer Safety Branch

Health Canada / Government of Canada

michelle.deveau@canada.ca / Tel: 613-948-8920

\*\*\*PLEASE NOTE MY NEW E-MAIL ADDRESS\*\*\*



Évaluatrice scientifique principale, Section d'évaluation des contaminants de l'air intérieur, Direction générale de la santé environnementale et de la sécurité des consommateurs

Santé Canada / Gouvernement du Canada michelle.deveau@canada.ca / Tél: 613-948-8920

\*\*\*VEUILLIEZ NOTER MON NOUVEAU ADRESSE COURRIEL\*\*\*



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 12/6/2017 2:28:37 PM

To: Robert Kavlock [rkavlock@gmail.com]
Subject: RE: 2 IRIS stories from Inside EPA

Attachments: IRIS-Interagency Meeting 25SEP17.pdf; IRIS BEST 100617\_2.pptx

We have it on slide 10 in the IRIS Interagency Workgroup Meeting. We also mentioned it a this NAS BEST meeting in the context of slide 8. If I find more, I'll send your way. Both slide decks are attached.

Tina

From: Robert Kavlock [mailto:rkavlock@gmail.com]
Sent: Wednesday, December 6, 2017 8:58 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Subject: Re: 2 IRIS stories from Inside EPA

## Ex. 5 - Deliberative Process

On Dec 6, 2017, at 7:26 AM, Bahadori, Tina < Bahadori. Tina@epa.gov> wrote:

## Ex. 5 - Deliberative Process

Tina

From: D'Amico, Louis

Sent: Tuesday, December 5, 2017 11:18 AM

To: Thayer, Kris <thayer.kris@epa.gov>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; Bahadori, Tina

<Bahadori.Tina@epa.gov>

Subject: Fwd: 2 IRIS stories from Inside EPA

FYI.

(202) 564-4605 (o)

Ex. 6 - Personal Privacy

Sent from my iPhone

(Please pardon brevity and typos)

Begin forwarded message:

From: "McGuinness, Moira" < McGuinness. Moira@epa.gov >

Date: December 5, 2017 at 11:15:34 AM EST

To: "D'Amico, Louis" < DAmico.Louis@epa.gov>, "Lehman, Rachel"



Cc: "Hubbard, Carolyn" < Hubbard. Carolyn@epa.gov>

Subject: 2 IRIS stories from Inside EPA

### <u>Industry Asks EPA To Consider Benefits, Endogenous Issue In IRIS</u> Analysis

Industry is urging EPA to consider additional issues in its upcoming analysis of the human health risks of exposure to nitrate and nitrite, including conducting a risk-benefit analysis of nitrate's dietary benefits, setting a policy on endogenous chemicals before completing the assessment, and reviewing the existing assessment of perchlorate.

Any one of these requests would greatly complicate EPA's assessment of nitrate and nitrite, one of three new Integrated Risk Information System (IRIS) assessments that the program's new leaders announced in September with scoping documents for public comment.

While EPA's Chemical Assessment Advisory Committee (CAAC), a subpanel of its Science Advisory Board, has been generally supportive of the agency's plans for the upcoming IRIS assessments, PepsiCo and the Western Growers' Association are arguing that EPA's plans were too narrow in scope.

PepsiCo's comments, for example, reminded EPA of the dietary benefits of eating vegetables, often high in nitrates.

"[A] complete evaluation of nitrate/nitrite should use an established method for the evaluation of benefit-risk, such as the benefit-risk analysis for foods ("Brafo"). Further, it is difficult to understand why the Agency has elected not to consider benefits in the assessment, particularly when it is acknowledged that environmental exposures (i.e., those that will be regulated using output from the IRIS assessment) to nitrates are minor contributors relative to dietary sources (~80%)," according to the Oct. 23 comments from PepsiCo's consultant, ToxStrategies. *The comments are available on insideEPA.com.* (Doc. ID: 207435)

"Without acknowledging benefits as part of a comprehensive evaluation, the potential for public confusion exists (e.g., should eating a healthy diet high in vegetable content be avoided because of the nitrate exposure?)."

ToxStrategies also urges EPA to consider risk-benefit assessments conducted by the European Food Safety Authority (EFSA) in addition to the 2017 assessment by the Agency for Toxic Substances and Disease Registry that EPA references in its scoping document for the analysis. EFSA's 2008 assessment of nitrates in vegetables concluded that the estimated exposures from eating the vegetables are unlikely to result in appreciable health risks, and therefore the recognized beneficial effects of consumption of vegetables prevail, ToxStrategies says. This holds true even in circumstances in which exposure to nitrates via vegetables alone would exceed the acceptable daily intake by slightly more than two-fold, the comments add.

EPA and the Food and Drug Administration considered using risk-benefit analysis to assess methylmercury, which contaminates some seafood. But the updated fish consumption advisory for women of childbearing age and children, released at the end of the Obama administration, did not rely on risk-benefit analysis.

EPA last assessed nitrate/nitrite in 1991, and in scoping documents for the upcoming assessment, the agency explains that "Since 1987, a growing body of literature indicates potential associations between nitrate/nitrite exposure and other noncancer health effects. Some epidemiological studies also suggest an increased risk of cancer, especially gastric cancer, associated with dietary nitrite exposure" (*Risk Policy Report*, Sept. 26).

ToxStrategies also pushes EPA to develop a policy on assessing the human health risks of an endogenous substance — one that exists naturally in the body, as well as being produced by commercial or industrial processes and potentially contaminating the environment, such as formaldehyde, methanol and nitrate.

As industry stakeholders argued with another endogenous chemical, methanol, ToxStrategies says EPA should develop such a policy before attempting the nitrate/nitrite assessment.

The American Chemistry Council (ACC) in 2013 urged EPA to hold a workshop on the endogenous issue, arguing that EPA should account for such endogenous levels or else the agency will set risk values at or below background levels, resulting in regulatory standards that will be difficult for industry to meet (*Risk Policy Report*, Oct. 22, 2013).

In its final 2013 assessment of methanol's non-cancer risks, EPA provided a novel analysis of how it differentiated between exogenous and endogenous exposures, but did not address the call for a broader endogenous policy (*Risk Policy Report*, Oct. 1, 2013).

ToxStrategies notes that EPA in its scoping document identifies "the role of endogenous and exogenous nitrate toxicity as a key scientific issue. Both endogenous and exogenous nitrate/nitrite are reduced to nitric oxide . . . essential for normal functioning of the brain, arteries, immune system, and others. The Agency has not routinely integrated endogenous/exogenous exposures into IRIS assessments, nor has the Agency developed guidance on how to do so. As such, the plan for differentiating exposures associated with normal physiological processes, such as maintenance of blood pressure, from exposures associated with potential adverse effects has not been



sufficiently addressed in the draft assessment plan. Further delineation and explanation of the plan for this complex topic is warranted — including an opportunity for the public to comment on such." Meanwhile, Western Growers, a trade group representing Arizona, California and Colorado fruit, nut and vegetable growers, is also urging EPA to expand its analyses, pressing the agency to reconsider its assessment of the rocket fuel perchlorate alongside the nitrate/nitrite assessment because they can have similar effects on the human thyroid hormone. EPA has been struggling for years to craft a health-based standard for perchlorate in drinking water, and is now operating under court-ordered deadlines to do so.

Western Growers remind EPA that perchlorate and nitrate/nitrite share the same health effect -- disruption of the thyroid -- and biological mode of action -- inhibiting the thyorid's ability to uptake iodine, which the thyorid needs to regulate properly.

"As USEPA proceeds with its IRIS nitrate/nitrite assessment, we believe it should also re-evaluate the inconsistency of a more conservative point of departure for perchlorate, especially in light of the fact that nitrate is known to account for much more of the [iodine uptake inhibition] burden at the thyroid than perchlorate. Moreover, re-evaluation of the perchlorate IRIS assessment should be a priority given that USEPA is currently considering the need for a National Primary Drinking Water Standard for perchlorate, and adoption of such standard could have widespread operational impacts on drinking water utilities and economic impacts on their customers. It could also undermine public confidence in the safety of foods containing low levels of perchlorate, leading to dietary changes that compromise public health."

The growers also urge EPA to consider an ongoing review of nitrate's health effects in drinking water by California's Office of Environmental Health Hazard Assessment (OEHHA). California's draft document "specifically concludes that thyroid effects should not be used as the basis for a revised [public health goal] due to a lack of consistency in study results, lack of adjustment for iodine status, possible measurement bias, and limitations in ecologic assessments of exposure. OEHHA's interpretation recognizes that these studies are not sufficiently robust to support risk assessment or risk-based regulatory decision-making." -- Maria Hegstad

### <u>Industry Arques TSCA Program Obviates Need For Ethylbezene IRIS</u> Analysis

An industry group is arguing that EPA's influential but controversial Integrated Risk Information System (IRIS) program should halt its plans to reassess ethlybenzene because the chemical is in line to be assessed by the new risk evaluation program required by the updated Toxic Substances Control Act (TSCA), and should be assessed by that program instead.

"The agency is required by statute to determine whether conditions of use for ethylbenzene present an unreasonable risk to human health or the environment based on a comprehensive, weight of the evidence review using the best available scientific information. An IRIS review is not a substitute for the TSCA Prioritization and Risk Evaluation processes," the Styrene Information and Research Council (SIRC) states in its Oct. 18 comments on draft scoping documents that EPA's IRIS program has prepared to update its 1991 assessment of ethylbenzene. The comments are available on InsideEPA.com. (Doc. ID: 207439)

The comments echo previous statements from industry stakeholders who questioned whether the IRIS program was relevant after Congress revised TSCA in the summer of 2016. Some longtime industry IRIS observers, many of whom have often criticized the IRIS program for producing what they consider to be overly strict risk analyses that they worry will lead to stringent regulations, argued that the new TSCA risk evaluation program will make the IRIS program redundant. The Obama EPA intended to continue the IRIS program, with that administration's toxics chief, Jim Jones, telling *Inside EPA* that the toxics office would rely on IRIS in conducting TSCA analyses, where IRIS assessments existed, because of the toxics office's limited risk assessment experience. But it is unclear how or whether the Trump EPA intends to incorporate the IRIS program. The president's fiscal year 2018 budget proposes greatly reducing its budget, while the Senate's proposed FY18 budget has language attached to it that would eliminate IRIS entirely. SIRC notes that "the TSCA amendments implement strict deadlines to ensure EPA is accountable in completing each step of the chemical risk evaluation process expeditiously, and requires EPA to complete an aggressive workload within these time frames."

The statute gives EPA one year to determine whether a chemical is high or low priority, and three years to complete an assessment of a chemical deemed high priority. To keep the assessments on track, the statute also requires that EPA must have underway at least 20 high priority substances by Dec. 22, 2019.

The IRIS program, housed in EPA's research office, does not have any statutory requirements, and was crafted by IRIS staff in the 1980s to ensure consistency in risk estimates across EPA offices and programs. The IRIS program has long focused on existing chemicals — those that were on the market when the original TSCA was enacted in 1976 and were largely grandfathered from regulation. These are the same group of chemicals — number unknown but anticipated in the tens of thousands — that the reformed TSCA directs EPA's chemicals office to assess.

**But SIRC suggests that for "a pragmatic approach to chemical risk assessment, ...** the IRIS Program office defer to the Office of Chemical Safety and Pollution Prevention, and perhaps provide support to the staff implementing risk evaluations under TSCA. . . . SIRC recommends that



EPA cease an unnecessary IRIS assessment and support the TSCA program to not only save the IRIS program significant time and resources, but ensure chemical reviews are performed efficiently and consistent with the strict standards" in the revised TSCA.

SIRC further argues that IRIS should cease its assessment of ethylbenzene because ethylbenzene is already controlled by regulations based on the existing IRIS assessment, which is stricter than necessary, the group states. SIRC argues that "the necessity of an IRIS review disappears when those regulations are based on health values that are protective or overly protective," such as the IRIS reference concentration and reference dose values, "and when the agency has conducted risk reviews and found the regulations to be protective of human health and the environment." SIRC in this case is citing a 2006 review of existing air regulations. EPA explains in its draft scoping document for ethylbenzene that the update was requested by several agency offices, including the Office of Land and Emergency Management (OLEM), multiple regional offices, Office of Air and Radiation (OAR), the water office and the toxics office, according to the recently released EPA documents.

IRIS staff conducted preliminary work to prepare for an ethylbenzene assessment in 2014. The IRIS program's new leaders, Kris Thayer and Tina Bahadori, stated in a September presentation that they confirmed with other agency offices that the chemical assessment is still a "current Agency need."

"As noted, measured human exposures of ethylbenzene in North America are low (generally <10 [parts per billion]), which is well below toxic effects of concern (750 [parts per million] tumors), and emissions of ethylbenzene have been declining. Industrial production of ethylbenzene accounts for less than 1% of exposure," SIRC says.

The group argues these figures plus conclusions in a 2015 publication and an earlier industry-backed assessment conducted through a voluntary Bush EPA program "demonstrate how the exposure, toxicology and risk information point to a single conclusion. EPA must indefinitely postpone, if not end, its IRIS review of ethylbenzene." — *Maria Hegstad* 

Moira

Moira McGuinness

EPA Research Editor in Chief
202-564-1507—desk

Ex. 6 - Personal Privacy —mobile

mcguinness.moira@epa.gov



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 9/8/2017 3:51:44 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]

CC: Ramasamy, Santhini [Ramasamy, Santhini@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]; Lavoie, Emma

[Lavoie.Emma@epa.gov]; Ross, Mary [Ross.Mary@epa.gov]; Hagerthey, Scot [Hagerthey.Scot@epa.gov]; Glenn,

Barbara [Glenn.Barbara@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

I want to think about what CAN be shared....

From: Kraft, Andrew

**Sent:** Friday, September 8, 2017 11:32 AM **To:** Bahadori, Tina <Bahadori.Tina@epa.gov>

**Cc:** Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Hagerthey, Scot <Hagerthey.Scot@epa.gov>; Glenn,

Barbara < Glenn. Barbara@epa.gov>

Subject: Fw: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

FYI. I was trying to avoid cc'ing everyone who weighed in on the outgoing email. Barbara and I plan to just have whichever managers participate on the phone call run things that need to be shared back up the management chain (I anticipate there will be nothing).

-Andrew

From: Kraft, Andrew

Sent: Friday, September 8, 2017 11:20 AM

To: Lidka Maslankiewicz

**Cc:** Els Smit; Paul Janssen; Joke Herremans; Glenn, Barbara; D'Amico, Louis; Bussard, David; Thayer, Kris **Subject:** Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Hi Lidka,

Barbara (Glenn) and I are the current chemical managers of the formaldehyde assessment. We were hoping we might be able to set up a phone conversation to talk through the current status of the assessment and your questions below? If so, I can send out some type of Google poll or similar to find a time that works for everyone who might want to participate?

I would emphasize to you that the draft you mention was never finalized after it was released for the purposes of peer consultation and review. Thus, it should not be cited as an EPA position. We can explain this in greater detail when we talk.

We look forward to future conversations, Andrew and Barbara



From: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl >

Sent: Tuesday, August 29, 2017 7:59 AM

To: Kraft, Andrew

Cc: Els Smit; Paul Janssen; Joke Herremans

Subject: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Dr Kraft,

My name is Lidka Maslankiewicz and I work at the Dutch National Institute for Public Health and the Environment (RIVM). We are currently busy with the update of the Maximum Permissible Risk (MPR) for formaldehyde.

We would like to use the approach and values described in IRIS Toxicological Review of Formaldehyde (Inhalation) (External Review Draft 2010), in particular Volume 3: "Quantitative Assessment, Major Conclusions in the Characterization of Hazard and Dose Response"

(<a href="https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614">https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614</a>), to derive MPR value for the Netherlands. Could you, please, inform me, if this could be permitted? Are there more recent versions of this document? If we would be allowed to use your data, how we could refer to the source?

## IRIS Toxicological Review of Formaldehyde (Inhalation ...

cfpub.epa.gov

EPA announces the release of the Toxicological Review of Formaldehyde-Inhalation Assessment in the June 2, 2010 Federal Register Notice. This draft assessment is ...

Kind regards
Lidka
Lidka Maslankiewicz
National Institute for Public Health and the Environment (RIVM)
Centre for Safety of Substances and Products
tel. 31 (0)30 2743160
+31 6 46 86 07 73
fax. 31 (0)30 2744401

e-mail: Lidka.Maslankiewicz@rivm.nl

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te melden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

www.rivm.ni De zorg voor morgen begint vandaag



|                                                                                                                                              | RIVM                                                                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                              | www.rivm.nl                                                                                                                                                               |
|                                                                                                                                              | Dit Nederlandse overheidsinstituut verzorgt informatie,<br>monitoring en wetenschappelijke onderbouwing van het<br>volksgezondheidsbeleid. Ook valt het informatiecentrum |
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| his message may contain information that                                                                                                     | is not intended for you. If you are not the addressee or if this message was sent to you by                                                                               |
| nistake, you are requested to inform the se<br>isks inherent in the electronic transmission<br>www.rivm.ni/en Committed to <i>health and</i> | inder and delete the message. RIVM accepts no liability for damage of any kind resulting from the of messages.                                                            |
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|                                                            |                             | Rijksinstituut                                                                                                                                                                             |
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|                                                            |                             | Volksgezondheid                                                                                                                                                                            |
|                                                            |                             | en Milieu - RIVM                                                                                                                                                                           |
|                                                            |                             | www.rivm.nl                                                                                                                                                                                |
|                                                            |                             | Dutch experts on<br>climate change<br>adaptation join forces.<br>Fourteen Dutch                                                                                                            |
|                                                            |                             | knowledge institutes<br>have joined forces to<br>provide practical,<br>demand-driven policy<br>advice based                                                                                |
|                                                            |                             |                                                                                                                                                                                            |



Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP From:

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

Sent: 10/6/2017 6:28:52 PM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; D'Amico, Louis

[DAmico.Louis@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

CC: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]

Subject: RE: Formaldehyde IRIS assessment

You are right, Barbara, let's give them the 18th and the 23rd and maybe one or two more with as many of us (but principally, you, Andrew, and David) and see where we land? T.

From: Glenn, Barbara

Sent: Thursday, October 5, 2017 11:31 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov> Cc: Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>

Subject: RE: Formaldehyde IRIS assessment

Looking at the calendars for Andrew, Tina, Kris and David, 8:30 am Oct 18th and 9:00 am Oct 23rd (excluding Kris) are possibilities, unless we figure out what we can say beforehand and only Andrew and I with David have to be on the call with RIVM.

How shall we try to set up a call with RIVM? I'm thinking it would be good to give them a few choices (morning times) -Barbara

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 5:26 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>

Cc: Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>

Subject: RE: Formaldehyde IRIS assessment

# Ex. 5 - Deliberative Process

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 5:01 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Bussard, David

<Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>

Subject: RE: Formaldehyde IRIS assessment

We have not yet set up the RIVM call. I believe there was a plan to discuss the RIVM call after the formaldehyde briefing on Monday and decide what would be okay to share, but the meeting to discuss did not happen. Maybe we still need to scope out what would be okay for Barbara and I to share prior to setting up either call?



Have a great weekend, Andrew

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 4:55 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; D'Amico, Louis < DAmico.Louis@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>

Cc: Ramasamy, Santhini <Ramasamy, Santhini@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>

Subject: RE: Formaldehyde IRIS assessment

I think set up a call to discuss. Do you have a call set up with RIVM already?

T.

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 4:52 PM

To: D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Bahadori, Tina

<<u>Bahadori.Tina@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Jones, Samantha

<Jones.Samantha@epa.gov>

Subject: FW: Formaldehyde IRIS assessment

Another request...

From: Deveau, Michelle (HC/SC) [mailto:michelle.deveau@canada.ca]

**Sent:** Thursday, September 28, 2017 4:10 PM **To:** Kraft, Andrew < <u>Kraft.Andrew@epa.gov</u>> **Subject:** Formaldehyde IRIS assessment

Hi Andrew,

We met briefly at your poster session at SOT 2016 (in New Orleans). I'm with the indoor air group at Health Canada, and we're thinking of reassessing our Residential Indoor Air Quality Guideline for formaldehyde. I was wondering if you'd be able to provide any information to me on your expected timelines for your IRIS assessment on formaldehyde. Are you still moving forward with updating your assessment? And do you have any approximate timelines on when you hope to have a draft published?

Your assessment is something that we would potentially be considering quite a bit if we did decide to reassess our guideline, so it would be very helpful if you are able to provide any possible information for us.

Thanks in advance for any information you can give me, Michelle

Michelle Deveau, MSc(A), ROH

Senior Scientific Evaluator, Indoor Air Contaminants Assessment Section, Healthy Environments and Consumer Safety Branch

Health Canada / Government of Canada

michelle.deveau@canada.ca / Tel: 613-948-8920



#### \*\*\*PLEASE NOTE MY NEW E-MAIL ADDRESS\*\*\*

Évaluatrice scientifique principale, Section d'évaluation des contaminants de l'air intérieur, Direction générale de la santé environnementale et de la sécurité des consommateurs

Santé Canada / Gouvernement du Canada

michelle.deveau@canada.ca / Tél: 613-948-8920

\*\*\*VEUILLIEZ NOTER MON NOUVEAU ADRESSE COURRIEL\*\*\*



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 1/30/2018 5:45:00 PM

**To**: Gwinn, Maureen [gwinn.maureen@epa.gov]

**Subject**: RE: Pruitt hearing

#### THANK YOU!

From: Gwinn, Maureen

**Sent:** Tuesday, January 30, 2018 12:42 PM **To:** Bahadori, Tina <Bahadori.Tina@epa.gov>

Subject: Re: Pruitt hearing

I did lose video briefly but I don't think it came up

Maureen R Gwinn PhD DABT
Office of Research and Development
US Environmental Protection Agency

(202)564-4621 office

Ex. 6 - Personal Privacy

On Jan 30, 2018, at 12:35 PM, Bahadori, Tina <Bahadori. Tina@epa.gov> wrote:

JOZ thought there would be an IRIS question....thanks for being our eyes and ears.

T>

From: Gwinn, Maureen

Sent: Tuesday, January 30, 2018 12:35 PM
To: Bahadori, Tina <Bahadori, Tina@epa.gov>

Subject: Re: Pruitt hearing

A lot on wotus too

Maureen R Gwinn PhD DABT Office of Research and Development US Environmental Protection Agency

(202)564-4621 office

Ex. 6 - Personal Privacy

On Jan 30, 2018, at 12:28 PM, Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>> wrote:

Thanks! Was he asked about IRIS, in general??

From: Gwinn, Maureen

Sent: Tuesday, January 30, 2018 12:21 PM

To: Jones, Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis

<<u>DAmico.Louis@epa.gov</u>>



**Cc:** Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Ross, Mary <<u>Ross, Mary@epa.gov</u>> **Subject:** Pruitt hearing

In case you are not watching - just a heads-up that the formaldehyde assessment was brought up by Senator Ed Markey at 12:15 or so in the hearing. He has asked for a response on the status within 10 days.

I know we'll get QFRs in full, but just wanted to pass this one along because 10 days is a short time frame.

Maureen R. Gwinn, PhD DABT ATS
Senior Science Advisor
National Center for Computational Toxicology
Office of Research and Development
1200 Pennsylvania Ave NW
MC 8101R
Washington, DC 20460

t(202)564-4621 f(202)565-2430 Ex. 6 - Personal Privacy



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 1/25/2018 5:37:34 PM

To: Axelrad, Daniel [Axelrad.Daniel@epa.gov]
Subject: RE: Meeting with ACC on Formaldehyde

Me too, Dan. I had not heard that she had joined Celanese! Thanks again, Dan. We are in a pretty tough space, but we are also PFAS coated ☺.

Tina

From: Axelrad, Daniel

**Sent:** Thursday, January 25, 2018 12:14 PM **To:** Bahadori, Tina <Bahadori.Tina@epa.gov> **Subject:** RE: Meeting with ACC on Formaldehyde

Hi Tina -

I'm happy to do anything I can to help the IRIS program, so don't hesitate with any requests like this. It was interesting – and I was surprised to see my former AA, Stephanie Daigle, at the meeting.

I'm looking forward to seeing the formaldehyde draft!

Thanks,

--Dan.

From: Bahadori, Tina

Sent: Wednesday, January 24, 2018 6:49 PM

To: Mazza, Carl < Mazza. Carl@epa.gov>; Sasser, Erika < Sasser. Erika@epa.gov>; Rimer, Kelly < Rimer. Kelly@epa.gov>;

Vasu, Amy <Vasu.Amy@epa.gov>; Axelrad, Daniel <Axelrad.Daniel@epa.gov>

Cc: Vandenberg, John < Vandenberg, John@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>; Lavoie, Emma

<<u>Lavoie.Emma@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Orme-

Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Subject: RE: Meeting with ACC on Formaldehyde

Dear OAR and OP colleagues,

When Jennifer Orme-Zavaleta asked that I invite you to this meeting, I was reluctant and worried that it might not be a good use of your time. I am sooooooooooo glad I listened to her. While it may not have been the best use of YOUR time, it was exceptionally important that we put forward a ONE EPA stance. THANK YOU for being there for us. And thanks for all your support along the way. Perhaps now, we will be able to move forward with Agency review of this important assessment. I know, hope springs eternal.

With warm regards,

Tina

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Tina Bahadori, Sc.D.



Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)
RRB Room 71210; Telephone: 202-564-7903; Mobile Ex. 6 - Personal Privacy



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 1/16/2018 2:41:51 PM

To: Axelrad, Daniel [Axelrad.Daniel@epa.gov]
Subject: RE: Meeting with ACC on Formaldehyde

#### THANK YOU!

From: Axelrad, Daniel

Sent: Tuesday, January 16, 2018 9:41 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Subject: RE: Meeting with ACC on Formaldehyde

Hi Tina -

I can attend on 1/24 from 2-3:00.

Thanks for the invite!

--Dan.

From: Bahadori, Tina

Sent: Tuesday, January 16, 2018 6:26 AM

To: Sasser, Erika <Sasser.Erika@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Axelrad, Daniel <Axelrad.Daniel@epa.gov>;

Mazza, Carl@epa.gov>

Cc: Ross, Mary <Ross.Mary@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>;

Vandenberg, John < Vandenberg, John @epa.gov >; Bussard, David @epa.gov >

Subject: RE: Meeting with ACC on Formaldehyde

Good Morning Everyone,

As you see below, ACC is coming in one more time to brief the Agency on their work on formaldehyde.

Ex. 5 - Deliberative Proces

#### Ex. 5 - Deliberative Process

Jennifer Orme-Zavaleta, ORD's Principal Deputy (acting AA, at times), asked if OAR and/or OP might be available to join us in this briefing. We can make a video connection available for RTP. If there are others we should invite, please let me know.

Thanks.

Tina

----Original Appointment-----

From: Orme-Zavaleta, Jennifer

Sent: Monday, December 4, 2017 1:55 PM

To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin;

Bahadori, Tina

Subject: Meeting with ACC on Formaldehyde

When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: DCRoomRRB41213/ORD

From: White, Kimberly [mailto:Kimberly\_White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM



To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21<sup>st</sup> letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22<sup>nd</sup> to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

+++++

<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA<sup>1</sup>, Gentry PR<sup>2</sup>, Dell LD<sup>2</sup>, Rodricks JV<sup>2</sup>, Boffetta P<sup>3</sup>. Author information

Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

#### **KEYWORDS:**

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology

++

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002

O: (202) 249-6707 C: (202) 341-7602

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From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 2/6/2018 11:38:37 AM

**To**: Thayer, Kris [thayer.kris@epa.gov]

Subject: RE: IRIS handbook

## Ex. 5 - Deliberative Process

As for the workshop, I have not heard anything from above yet. But ACC put out their news release and Ex. 5 - Deliberative Process

So, let's see how it all unfolds.

## Ex. 5 - Deliberative Process

Τ.

From: Thayer, Kris

**Sent:** Tuesday, February 6, 2018 6:28 AM **To:** Bahadori, Tina <Bahadori.Tina@epa.gov>

Subject: RE: IRIS handbook

Agree...

### Ex. 5 - Deliberative Process

Have you heard any response to NAS from IOAA and above?

From: Bahadori, Tina

**Sent:** Tuesday, February 6, 2018 6:26 AM **To:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>>

Subject: RE: IRIS handbook

## Ex. 5 - Deliberative Process

Τ.

From: Thayer, Kris

**Sent:** Tuesday, February 6, 2018 6:23 AM **To:** Bahadori, Tina < <u>Bahadori, Tina@epa.gov</u>>

Subject: RE: IRIS handbook

I don't think so, especially given the focus on the epi data. NAS did say not to stop until everything was perfect.

From: Bahadori, Tina

Sent: Tuesday, February 6, 2018 6:19 AM



To: Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: IRIS handbook

OK.... Ex. 5 - Deliberative Process

From: Thayer, Kris

**Sent:** Tuesday, February 6, 2018 6:12 AM **To:** Bahadori, Tina <a href="mailto:8ahadori.Tina@epa.gov">8ahadori.Tina@epa.gov</a>

Subject: RE: IRIS handbook

## Ex. 5 - Deliberative Process

From: Bahadori, Tina

**Sent:** Tuesday, February 6, 2018 6:06 AM **To:** Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: IRIS handbook

A couple of things –

1)

2)

Ex. 5 - Deliberative Process

Τ.

From: Thayer, Kris

**Sent:** Tuesday, February 6, 2018 6:00 AM **To:** Bahadori, Tina < Bahadori, Tina@epa.gov>

Subject: Re: IRIS handbook

Understood. We will work to make the timeline feasible from document production side and see how it all shakes out mid-March

Sent from my iPhone

On Feb 6, 2018, at 5:58 AM, Bahadori, Tina <a href="mailto:Sahadori.Tina@epa.gov">Bahadori.Tina@epa.gov</a>> wrote:

## Ex. 5 - Deliberative Process

From: Thayer, Kris

**Sent:** Tuesday, February 6, 2018 4:53 AM **To:** Bahadori, Tina <a href="mailto:8ahadori.Tina@epa.gov">8ahadori.Tina@epa.gov</a>

Subject: IRIS handbook



# Ex. 5 - Deliberative Process

Kristina Thayer, Ph.D.

Director, Integrated Risk Information System (IRIS) Division National Center for Environmental Assessment, NCEA ORD, USEPA

Mail Code: B243-01

Building: Bldg B (Room B211I) Research Triangle Park, NC 27711

(919) 541-0152 RTP

(202) 564-1771 Ronald Reagan Building (room 51203)

Skype: kristina.thayer thayer.kris@epa.gov



From: White, Kimberly [Kimberly\_White@americanchemistry.com]

**Sent**: 8/11/2017 11:08:33 AM

To: Thayer, Kris [thayer.kris@epa.gov]; Bahadori, Tina [Bahadori.Tina@epa.gov]

Subject: RE: Invitation to Attend Invited Experts Workshop on Formaldehyde

Sure. I'll plan to give you a call at 1pm instead then.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly\_White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602

www.americanchemistry.com

**From:** Thayer, Kris [mailto:thayer.kris@epa.gov]

**Sent:** Friday, August 11, 2017 7:08 AM **To:** White, Kimberly; Bahadori, Tina

Subject: RE: Invitation to Attend Invited Experts Workshop on Formaldehyde

Thanks! Can we make it closer to 12:30 or 1? I have a meeting ending at 12:00 that I suspect may run a little long.

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Friday, August 11, 2017 6:33 AM

**To:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>>; Bahadori, Tina <a href="mailto:Bahadori.Tina@epa.gov">Bahadori.Tina@epa.gov</a>></a>
<a href="mailto:Subject: RE: Invitation to Attend Invited Experts Workshop on Formaldehyde">Bahadori.Tina@epa.gov</a>>

Dear Kris:

Great. I will plan to give you a call at ~12:15pm (ET). I look forward to speaking with you.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com

From: Thayer, Kris [mailto:thayer.kris@epa.gov]
Sent: Thursday, August 10, 2017 8:03 PM

**To:** White, Kimberly; Bahadori, Tina

Subject: RE: Invitation to Attend Invited Experts Workshop on Formaldehyde

Kimberly,

I will be available to attend – I'm free between 12 and 2 pm tomorrow if you want to discuss [Ex. 6 - Personal Privacy.]. Does that time window work for you?

Sincerely,

Kris



-----

Kristina Thayer, Ph.D.

Director, Integrated Risk Information System (IRIS) Division National Center for Environmental Assessment, NCEA

ORD, USEPA

Mail Code: B243-01

Building: Bldg B (Room B211I) Research Triangle Park, NC 27711

(919) 541-0152 RTP

(703) 347-0260 Potomac Yards

Skype: kristina.thayer <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Wednesday, August 2, 2017 11:02 AM

To: Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer, Kris @epa.gov</a>>

Subject: Invitation to Attend Invited Experts Workshop on Formaldehyde

Dear Dr. Bahadori and Dr. Thayer,

I am assisting in the coordination of a 1 ½ day invited experts workshop of ~25 scientist in October 2017. The focus of the workshop will be to explore the formaldehyde science and discuss approaches for evaluating and integrating the available evidence to draw conclusions regarding human health cancer risk. Dr. Jim Swenberg and Dr. Ken Mundt have agreed to chair the workshop and we've extended invitations to a broad range of scientists from academia, industry and government. Given your activities on formaldehyde, you and your staff would be welcomed additions to the workshop and I'd like to discuss your interest and availability in participating. The workshop is tentatively planned to take place in Chapel Hill, NC and is targeted for October 10 - 11, 2017. I am working with the workshop chairs to confirm attendance to the workshop and would welcome the opportunity to discuss the tentative agenda topics and attendee list.

Feel free to give me a call (202-249-6707) or email (<u>kimberly\_white@americanchemistry.com</u>) at your convenience to discuss further or let me know a good time to give you a call. Thank you for considering this invitation and I look forward to speaking with you.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com





From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 9/22/2017 10:58:04 AM

**To**: Thayer, Kris [thayer.kris@epa.gov]

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Here is my thought:

## Ex. 5 - Deliberative Process

T.

From: Thayer, Kris

**Sent:** Friday, September 22, 2017 6:42 AM **To:** Bahadori, Tina <Bahadori.Tina@epa.gov>

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Thanks for the background and ugh on timeline.

# Ex. 5 - Deliberative Process

I'm thinking we need to have the Monday briefing before we can respond to RIVM?

From your mail, we understand that the information is not to be cited as the EPA position. That was not our intention, but rather we want to include the unit risks as a scientific approach that has been developed and that we need to take on board.

Could it be possible to use the information, if we explicitly include a disclaimer? Something in line with: "It should be noted that the methodology used for the quantification of cancer risk for NPC (Nasopharyngeal Cancer), has not been formalised and should not be seen as the official position of the EPA. From a scientific viewpoint, however, we consider this approach as valid and use unit risk to derive the Maximum Permissible Risk (MPR)."

From: Bahadori, Tina

**Sent:** Friday, September 22, 2017 6:36 AM **To:** Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

How likely? I am going to go for it in full tiger mama form, but I don't know if it will be possible. Lou will likely say not.



I have mentioned to Barbara and Andrew at different times, but I don't know if they necessarily thought this would even be possible. I have also talked to Andrew about the possibility of sharing the overview document with RIVM. But I have not mentioned to David. We will assess all of this after Monday's briefing.

## Ex. 5 - Deliberative Process

This request from RIVM, I think we can respond to it and somehow accommodate it, no?? Is there resistance??

T.

From: Thayer, Kris

Sent: Friday, September 22, 2017 5:00 AM To: Bahadori, Tina <Bahadori.Tina@epa.gov>

Subject: FW: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

How likely do you think it is that we will be able to share the FA overview document as part of NAS review?

Do David, Andrew, Barbara and others know that is something that is being explored?

From: Lidka Maslankiewicz [mailto:lidka.maslankiewicz@rivm.nl]

Sent: Friday, September 22, 2017 4:54 AM To: Kraft, Andrew < Kraft. Andrew@epa.gov>

Cc: Bussard, David <Bussard.David@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Els Smit <els.smit@rivm.nl>;

Glenn, Barbara <Glenn.Barbara@epa.gov>; Joke Herremans <joke.herremans@rivm.nl>; Paul Janssen <paul.janssen@rivm.nl>; Thayer, Kris <thayer.kris@epa.gov>; Theo Vermeire <theo.vermeire@rivm.nl>

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Andrew and Barbara

Thank you for your reply, apologies for not answering sooner.

The issue is that we would like to use the data as presented in the 2010 Draft, more specifically the quantification of cancer risks for NPC (Nasopharyngeal Cancer), based either on human data and on animal data.

From your mail, we understand that the information is not to be cited as the EPA position. That was not our intention, but rather we want to include the unit risks as a scientific approach that has been developed and that we need to take on board.

Could it be possible to use the information, if we explicitly include a disclaimer? Something in line with: "It should be noted that the methodology used for the quantification of cancer risk for NPC (Nasopharyngeal Cancer), has not been formalised and should not be seen as the official position of the EPA. From a scientific viewpoint, however, we consider this approach as valid and use unit risk to derive the Maximum Permissible Risk (MPR)."

We also noted that in 2014 US-EPA convened a workshop (https://www.epa.gov/sites/production/files/2014-12/documents/formaldehyde workshop agenda final.pdf), the topics of which were the endogenous formation of formaldehyde and its relation to formaldehyde toxicity and the mechanistic evidence for lymphohematopoietic cancer induction by formaldehyde. Any further information on these topics and on the envisaged timeline for finalization of the US-EPA IRIS evaluation would be very welcome.

Maybe we can first do the exchange via mail and decide later on if a telephone conference is useful.



#### Kind regards

Lidka

Lidka Maslankiewicz National Institute for Public Health and the Environment (RIVM) Centre for Safety of Substances and Products tel. 31 (0)30 2743160 +31 6 46 86 07 73

fax. 31 (0)30 2744401

e-mail: Lidka.Maslankiewicz@rivm.nl

From: "Kraft, Andrew" < Kraft. Andrew@epa.gov >

To: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl >,

Cc: Els Smit <<u>els.smit@rivm.nl</u>>, Paul Janssen <<u>paul.janssen@rivm.nl</u>>, "Joke Herremans" <<u>joke.herremans@rivm.nl</u>>, "Glenn, Barbara"

< Glenn.Barbara@epa.gov>, "D'Amico, Louis" < DAmico.Louis@epa.gov>, "Bussard, David" < Bussard.David@epa.gov>, "Thayer, Kris" < thayer.kris@epa.gov>

Date: 09/08/2017 05:21 PM

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Hi Lidka,

Barbara (Glenn) and I are the current chemical managers of the formaldehyde assessment. We were hoping we might be able to set up a phone conversation to talk through the current status of the assessment and your questions below? If so, I can send out some type of Google poll or similar to find a time that works for everyone who might want to participate?

I would emphasize to you that the draft you mention was never finalized after it was released for the purposes of peer consultation and review. Thus, it should not be cited as an EPA position. We can explain this in greater detail when we talk.

We look forward to future conversations, Andrew and Barbara

From: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl>

Sent: Tuesday, August 29, 2017 7:59 AM

To: Kraft, Andrew

Cc: Els Smit; Paul Janssen; Joke Herremans

Subject: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Dr Kraft,

My name is Lidka Maslankiewicz and I work at the Dutch National Institute for Public Health and the Environment (RIVM). We are currently busy with the update of the Maximum Permissible Risk (MPR) for formaldehyde.

We would like to use the approach and values described in IRIS Toxicological Review of Formaldehyde (Inhalation) (External Review Draft 2010), in particular Volume 3: "Quantitative Assessment, Major Conclusions in the Characterization of Hazard and Dose Response"



(<u>https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614</u>), to derive MPR value for the Netherlands. Could you, please, inform me, if this could be permitted? Are there more recent versions of this document? If we would be allowed to use your data, how we could refer to the source?

## IRIS Toxicological Review of Formaldehyde (Inhalation ...

cfpub.epa.gov

EPA announces the release of the Toxicological Review of Formaldehyde-Inhalation Assessment in the June 2, 2010 Federal Register Notice. This draft assessment is ...

Kind regards
Lidka
Lidka Maslankiewicz
National Institute for Public Health and the Environment (RIVM)
Centre for Safety of Substances and Products
tel. 31 (0)30 2743160
+31 6 46 86 07 73

e-mail: Lidka.Maslankiewicz@rivm.nl

fax. 31 (0)30 2744401

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| Dutch experts on climate change adaptation join forces. Fourteen Dutch      |
| knowledge institutes have joined forces to provide practical, demand-driven |
| policy advice based                                                         |

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| informatiecentrum                                                           |

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|-----------------------------------------------------------------------------|
| www.rivm.nl                                                                 |
| Dutch experts on climate change adaptation join forces. Fourteen Dutch      |
| knowledge institutes have joined forces to provide practical, demand-driven |
| policy advice based                                                         |

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te melden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

www.rivm.ni De zorg voor morgen begint vandaag

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From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 9/29/2017 4:42:48 AM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; D'Amico, Louis

[DAmico.Louis@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

CC: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Jones, Samantha [Jones.Samantha@epa.gov]

**Subject**: RE: Formaldehyde IRIS assessment

Great. Thanks.

Tina

From: Glenn, Barbara

Sent: Thursday, September 28, 2017 5:36 PM

**To:** Bahadori, Tina <Bahadori.Tina@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov> **Cc:** Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>

Subject: RE: Formaldehyde IRIS assessment

Next week Andrew and I can work on setting up the two calls while we figure out what we can say to them.

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 5:26 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; D'Amico, Louis < DAmico.Louis@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>

**Cc:** Ramasamy, Santhini < <u>Ramasamy.Santhini@epa.gov</u>>; Glenn, Barbara < <u>Glenn.Barbara@epa.gov</u>>; Jones, Samantha

<Jones.Samantha@epa.gov>

Subject: RE: Formaldehyde IRIS assessment

# Ex. 5 - Deliberative Process

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 5:01 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>

Cc: Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Jones, Samantha

<Jones.Samantha@epa.gov>

Subject: RE: Formaldehyde IRIS assessment

We have not yet set up the RIVM call. I believe there was a plan to discuss the RIVM call after the formaldehyde briefing on Monday and decide what would be okay to share, but the meeting to discuss did not happen. Maybe we still need to scope out what would be okay for Barbara and I to share prior to setting up either call?

Have a great weekend,

Andrew

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 4:55 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; D'Amico, Louis < DAmico.Louis@epa.gov>; Bussard, David



<<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>

 $\textbf{Cc:} \ Ramasamy, Santhini < \underline{Ramasamy.Santhini@epa.gov} >; \ Glenn, \ Barbara < \underline{Glenn.Barbara@epa.gov} >; \ Jones, \ Samantha < \underline{Glenn.Bar$ 

<Jones.Samantha@epa.gov>

Subject: RE: Formaldehyde IRIS assessment

I think set up a call to discuss. Do you have a call set up with RIVM already?

T.

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 4:52 PM

To: D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Bahadori, Tina

<Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Jones, Samantha

<Jones.Samantha@epa.gov>

Subject: FW: Formaldehyde IRIS assessment

Another request...

From: Deveau, Michelle (HC/SC) [mailto:michelle.deveau@canada.ca]

**Sent:** Thursday, September 28, 2017 4:10 PM **To:** Kraft, Andrew < <u>Kraft.Andrew@epa.gov</u>> **Subject:** Formaldehyde IRIS assessment

Hi Andrew,

We met briefly at your poster session at SOT 2016 (in New Orleans). I'm with the indoor air group at Health Canada, and we're thinking of reassessing our Residential Indoor Air Quality Guideline for formaldehyde. I was wondering if you'd be able to provide any information to me on your expected timelines for your IRIS assessment on formaldehyde. Are you still moving forward with updating your assessment? And do you have any approximate timelines on when you hope to have a draft published?

Your assessment is something that we would potentially be considering quite a bit if we did decide to reassess our guideline, so it would be very helpful if you are able to provide any possible information for us.

Thanks in advance for any information you can give me, Michelle

Michelle Deveau, MSc(A), ROH

Senior Scientific Evaluator, Indoor Air Contaminants Assessment Section, Healthy Environments and Consumer Safety Branch

Health Canada / Government of Canada

michelle.deveau@canada.ca / Tel: 613-948-8920

\*\*\*PLEASE NOTE MY NEW E-MAIL ADDRESS\*\*\*

Évaluatrice scientifique principale, Section d'évaluation des contaminants de l'air intérieur, Direction générale de la santé environnementale et de la sécurité des consommateurs

Santé Canada / Gouvernement du Canada

michelle.deveau@canada.ca / Tél: 613-948-8920

\*\*\*VEUILLIEZ NOTER MON NOUVEAU ADRESSE COURRIEL\*\*\*





From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 10/26/2017 10:02:34 AM

To: Sjogren, Mya [Sjogren.Mya@epa.gov]; Fleming, Megan [Fleming.Megan@epa.gov]

**Subject**: Thursday's Formaldehyde Science Discussion

Dear Mya and Megan,

The team is going to come to RRB for this meeting – so we won't need a video to my office.

Thanks,

Tina

-----Original Appointment-----

From: Sjogren, Mya On Behalf Of Rodan, Bruce Sent: Wednesday, October 25, 2017 11:45 AM

To: Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming, Megan

Subject: Formaldehyde Science Discussion

When: Thursday, November 2, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41226 RRB/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

- Barbara Glenn
- Andrew Kraft
- Tom Bateson
- Kris Thayer

At first glance Tuesday 10/31/17 at noon looks good © on everyone's calendar. Hopefully we can snag that soon!!

Thanks,

Tina



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 2/7/2018 2:06:36 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

Subject: RE: Workshop

Ex. 5 - Deliberative Process I just gave my feedback to David. Let's see where it goes from

here.

Т.

From: Kraft, Andrew

Sent: Wednesday, February 7, 2018 8:01 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Subject: Re: Workshop

# Ex. 6 - Personal Privacy

# Ex. 5 - Deliberative Process

Talk to you soon, Andrew

From: Bahadori, Tina

Sent: Wednesday, February 7, 2018 7:54 AM

To: Kraft, Andrew; Thayer, Kris

Subject: RE: Workshop

Understood. We will caveat as we move forward. How are you feeling?

T.

From: Kraft, Andrew

Sent: Wednesday, February 7, 2018 7:52 AM

To: Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer, Kris < a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>

Subject: Re: Workshop

# Ex. 5 - Deliberative Process



From: Thayer, Kris

Sent: Tuesday, February 6, 2018 8:27 PM

To: Bahadori, Tina; Avery, James; Soto, Vicki; Shams, Dahnish; Kraft, Andrew

Subject: RE: Workshop

Yes, this was a good one!

From: Bahadori, Tina

Sent: Tuesday, February 6, 2018 8:07 AM

To: Thayer, Kris <<a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>; Avery, James <a href="mailto:Avery.James@epa.gov">Avery.James@epa.gov</a>; Soto, Vicki <a href="mailto:Soto.Vicki@epa.gov">Soto, Vicki <a href="mailto:Soto.Vicki@epa.gov">Soto.Vicki@epa.gov</a>;

Shams, Dahnish < Shams. Dahnish@epa.gov >; Kraft, Andrew < Kraft. Andrew@epa.gov >

Subject: Workshop

A good one from inside EPA.

#### Begin forwarded message:

From: InsideEPA.com < insideepa-alerts@iwpnews.com >

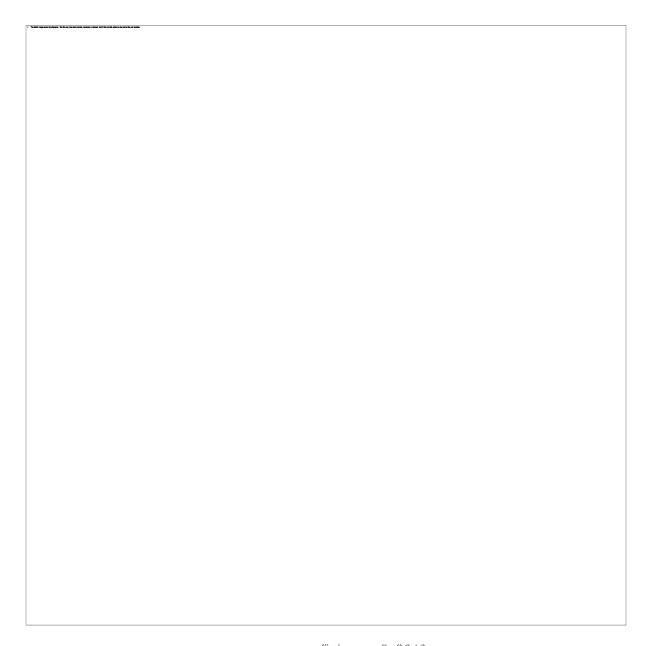
**Date:** February 6, 2018 at 7:50:01 AM EST

To: <bahadori.tina@epa.gov>

Subject: Risk Policy Report - Latest Issue Now Available

Reply-To: <insideepa-alerts@iwpnews.com>





February 6, 2018

Now available: The latest issue of Risk Policy Report.

**Top Stories** 

#### IRIS Staff Seek To Defend Program From Industry Challenges In NAS Review

Top staff leaders of EPA's embattled Integrated Risk Information System (IRIS) are defending the program and outlining progress they say has been made to address past critiques from the National Academy of Sciences (NAS) and others, in the face of industry's ongoing criticism and questions over the program's future at the agency.

#### Peer Reviewers Call EPA Perchlorate Model Best Of Imperfect Alternatives

Scientists peer reviewing EPA's latest version of a model intended to aid the agency in setting a national drinking water standard for the rocket fuel ingredient perchlorate appeared to deem it the



best option among a handful of imperfect alternatives, even as some stakeholders suggested EPA return to an approach proposed years ago.

#### ACC Urges EPA To Revise PBT Criteria Over Environmentalists' Objections

The American Chemistry Council (ACC) is urging EPA to update its criteria for identifying persistent, bioaccumulative and toxic (PBT) chemicals under the revised Toxic Substances Control Act (TSCA), calling the criteria "outdated" and failing to reflect current science.

#### Industry Backs EPA's New Chemicals Framework But Seeks Faster Reviews

Chemical industry groups are backing EPA's authority to drop the use of enforceable orders as an interim step in its framework for regulating new chemicals under the revised Toxic Substances Control Act (TSCA), arguing the agency has used the approach in the past, but are also urging EPA to take further steps to speed its new chemical review process.



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Mailing address: 1919 South Eads Street, Suite 201, Arlington VA 22202

Telephone: 703-416-8500 or 1-800-424-9068

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From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 1/23/2018 7:24:15 AM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]
BCC: Tina Bahadori Ex. 6 - Personal Privacy

**Subject**: tracking the evolution of formaldehyde briefings

Attachments: FW: Follow-up; RE: Formaldehyde Science Invited Expert Workshop; FW: Submission of Letter on Behalf of the ACC

Formaldehyde Panel; Letter Submitted on Behalf of the ACC Formaldehyde Panel; Next Steps on Formaldehyde IRIS

Assessment

# Ex. 5 - Deliberative Process



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 10/23/2017 12:08:59 PM

To: Bussard, David [Bussard.David@epa.gov]
Subject: RE: Caffeine and formaldehyde task

OK, then, see what he says.

T.

From: Bussard, David

**Sent:** Monday, October 23, 2017 8:08 AM **To:** Bahadori, Tina <Bahadori.Tina@epa.gov> **Subject:** Re: Caffeine and formaldehyde task

I'll ask Bruce. (Kris said she had stepped out during that part of the discussion.)

David Bussard

On Oct 23, 2017, at 7:21 AM, Bahadori, Tina < Bahadori. Tina@epa.gov > wrote:

Hi David,

It's no problem to ask Bruce, but do you want to ask Kris first?

١.

From: Bussard, David

**Sent:** Monday, October 23, 2017 7:19 AM **To:** Bahadori, Tina < <u>Bahadori.Tina@epa.gov</u>> **Subject:** Fwd: Caffeine and formaldehyde task

Tina

It would be useful to know what ACC's caffeine argument is. Are you okay if I ask Bruce? Would you rather ask him or would you rather we guess what their argument is or ask Iris Camacho?

David Bussard

Begin forwarded message:

From: "Thayer, Kris" < thayer.kris@epa.gov > Date: October 22, 2017 at 7:48:54 AM EDT

To: "Ramasamy, Santhini" < Ramasamy, Santhini@epa.gov>

Cc: "Bussard, David" < Bussard. David@epa.gov>, "Keshava, Nagalakshmi"

<Keshava.Nagu@epa.gov>

Subject: RE: Caffeine and formaldehyde task

I had to step out of the meeting for a call while some of this discussion was happening – should we share your question with Bruce and Iris, who were also present at the meeting?



From: Ramasamy, Santhini

**Sent:** Friday, October 20, 2017 1:16 PM **To:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>>

Cc: Bussard, David <Bussard.David@epa.gov>; Keshava, Nagalakshmi

<<u>Keshava.Nagu@epa.gov</u>>

**Subject:** RE: Caffeine and formaldehyde task

## Ex. 5 - Deliberative Process

I am thinking loud here. Thank you letting me know that there were no slides.

From: Thayer, Kris

**Sent:** Friday, October 20, 2017 12:58 PM

To: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>

Cc: Bussard, David < Bussard. David@epa.gov >; Keshava, Nagalakshmi

<Keshava.Nagu@epa.gov>

Subject: RE: Caffeine and formaldehyde task

Yes, I was at the meeting. The issue was the caffeine as a source of exposure. I don't have slides though.

Does this help?

From: Ramasamy, Santhini

Sent: Friday, October 20, 2017 11:34 AM To: Thayer, Kris <thayer.kris@epa.gov>

Cc: Bussard, David <Bussard. David@epa.gov>; Keshava, Nagalakshmi

<Keshava.Nagu@epa.gov>

**Subject:** FW: Caffeine and formaldehyde task

Hi Kris,

I have a question about formaldehyde formation during caffeine metabolism. I heard from David that ACC had a presentation in one of the meetings making an argument. Were you at the meeting? If so, do you happen to have the slides or remember their argument? Please share it with Nagu since I have tasked Nagu to look into this.

Thank you for your help.

Santhini



From: Ramasamy, Santhini

Sent: Thursday, October 19, 2017 4:02 PM

To: Keshava, Nagalakshmi < Keshava. Nagu@epa.gov>

Subject: RE: Caffeine and formaldehyde task

Okay, can you send me half hour invite to talk about this tomorrow?

From: Keshava, Nagalakshmi

Sent: Thursday, October 19, 2017 3:21 PM

To: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>

Subject: RE: Caffeine and formaldehyde task

Hi Santhini,

Can we have a chat tomorrow morning? I will look into the topic and see what I come up with, in the meantime, I might need more information as to what exactly you are looking for. Let's talk tomorrow to get a better idea.

Thanks nagu

From: Ramasamy, Santhini

Sent: Thursday, October 19, 2017 2:57 PM

To: Keshava, Nagalakshmi < Keshava. Nagu@epa.gov>

Subject: Caffeine and formaldehyde task

Hi Nagu,

## Ex. 5 - Deliberative Process

Thanks.

Santhini



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 1/19/2018 4:25:22 PM

To: Sasser, Erika [Sasser.Erika@epa.gov]; Vandenberg, John [Vandenberg.John@epa.gov]; Vasu, Amy

[Vasu.Amy@epa.gov]; Axelrad, Daniel [Axelrad.Daniel@epa.gov]; Mazza, Carl [Mazza.Carl@epa.gov]

CC: Ross, Mary [Ross.Mary@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Thayer, Kris [thayer.kris@epa.gov];

Bussard, David [Bussard.David@epa.gov]; Rimer, Kelly [Rimer.Kelly@epa.gov]

**Subject**: RE: Meeting with ACC on Formaldehyde

Thank you very much. I will make sure you are on the calendar invite. Other names are not required, unless they are going to join separately and need their own calendar invite.

Tina

From: Sasser, Erika

Sent: Friday, January 19, 2018 11:16 AM

**To:** Bahadori, Tina <Bahadori.Tina@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Axelrad, Daniel <Axelrad.Daniel@epa.gov>; Mazza, Carl <Mazza.Carl@epa.gov>

Cc: Ross, Mary <Ross.Mary@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>;

Bussard, David <Bussard.David@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>

Subject: RE: Meeting with ACC on Formaldehyde

Tina, yes we plan to attend. Kelly Rimer, Amy Vasu and I will join John and others in RTP videoconference room B249. Do you need a list of names, if others in OAR express interest in attending?

**Thanks** 

From: Bahadori, Tina

Sent: Tuesday, January 16, 2018 9:18 AM

To: Vandenberg, John < \(\frac{Vandenberg\_John@epa\_gov}\); Sasser, Erika < \(\frac{Sasser\_Erika@epa\_gov}\); Vasu, Amy \(<\frac{Vasu\_Amy@epa\_gov}\); Axelrad, Daniel < \(\frac{Axelrad\_Daniel@epa\_gov}\); Mazza, Carl < \(\frac{Mazza\_Carl@epa\_gov}\)

Cc: Ross, Mary <Ross.Mary@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>;

Bussard, David < Bussard. David@epa.gov>

Subject: RE: Meeting with ACC on Formaldehyde

Thanks John – OAR/OP, please let me know if you WILL be able to attend so that I can let Jennifer know. Tina

From: Vandenberg, John

Sent: Tuesday, January 16, 2018 7:57 AM

To: Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Sasser, Erika <<u>Sasser, Erika@epa.gov</u>>; Vasu, Amy <<u>Vasu, Amy@epa.gov</u>>;

Axelrad, Daniel <<u>Axelrad.Daniel@epa.gov</u>>; Mazza, Carl <<u>Mazza.Carl@epa.gov</u>>

Cc: Ross, Mary <Ross.Mary@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>;

Bussard, David < Bussard. David@epa.gov>

Subject: RE: Meeting with ACC on Formaldehyde

I have reserved B249 for a video connection to RTP from 2-3 on 1/24 -- OAQPS is welcome to join us for this meeting with ACC.

John



From: Bahadori, Tina

Sent: Tuesday, January 16, 2018 6:26 AM

To: Sasser, Erika <Sasser.Erika@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Axelrad, Daniel <Axelrad.Daniel@epa.gov>;

Mazza, Carl@epa.gov>

Cc: Ross, Mary <Ross.Mary@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>;

Vandenberg, John < Vandenberg, John@epa.gov>; Bussard, David < Bussard, David@epa.gov>

Subject: RE: Meeting with ACC on Formaldehyde

Good Morning Everyone,

As you see below, ACC is coming in one more time to brief the Agency on their work on formaldehyde Ex.5-Deliberative Process

Ex. 5 - Deliberative Process

to join us in this briefing. We can make a video connection available for RTP. If there are others we should invite, please let me know.

Thanks,

Tina

-----Original Appointment-----

From: Orme-Zavaleta, Jennifer

Sent: Monday, December 4, 2017 1:55 PM

To: Orme-Zavaleta, Jennifer; Rodan, Bruce; Yamada, Richard (Yujiro); Fleming, Megan; Christian, Megan; Kuhn, Kevin;

Bahadori, Tina

Subject: Meeting with ACC on Formaldehyde

When: Wednesday, January 24, 2018 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: DCRoomRRB41213/ORD

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21<sup>st</sup> letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22<sup>nd</sup> to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

+++++

<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

<u>Mundt KA<sup>1</sup></u>, <u>Gentry PR<sup>2</sup></u>, <u>Dell LD<sup>2</sup></u>, <u>Rodricks JV<sup>2</sup></u>, <u>Boffetta P<sup>3</sup></u>. **Author information** 

Abstract



Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" (NRC 2011). They offered recommendations for improving the IRISreview and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

#### **KEYWORDS:**

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology

++

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com



From: Bahadori, Tina [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7DA7967DCAFB4C5BBC39C666FEE31EC3-BAHADORI, TINA]

**Sent**: 9/15/2017 11:19:25 PM

**To**: Sasser, Erika [Sasser.Erika@epa.gov]

CC: Thayer, Kris [thayer.kris@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Rimer, Kelly [Rimer.Kelly@epa.gov];

Vasu, Amy [Vasu.Amy@epa.gov]; Vandenberg, John [Vandenberg.John@epa.gov]

**Subject**: Re: IRIS Assessment for Formaldehyde

Hi Erika,

Thank you for your message. We would be very pleased to provide a status briefing on formaldehyde, and will work to have that scheduled in early October.

For your information, we will be presenting our recent efforts to modernize IRIS as well as three nascent assessments to the SAB Chemical Assessment Advisory Committee (SAB-CAAC) on 27-28 September. One of those assessments is ethylbenzene. We will preview this work to the STPC at their next meeting on 9/20.

Please let us know if you would like additional information about any of these.

Have a wonderful weekend.

Tina

On Sep 15, 2017, at 11:16 AM, Sasser, Erika <<u>Sasser, Erika@epa.gov</u>> wrote:

Hi Tina,

I'm interested in following up with you about the status of the IRIS assessment for formaldehyde. As you know, we have a strong interest in this because of formaldehyde's importance as an air toxic in both NATA and the RTR program. We are very pleased to hear that the new assessment is nearing completion and would very much like to have a meeting with you where you walk us through the assessment. If this is possible, perhaps Emma can work with Amy Vasu of my staff to set up such a meeting. We look forward to hearing about the results.

Thanks, Erika

Erika N. Sasser, Ph.D.
Director, Health and Environmental Impacts Division
Office of Air Quality Planning & Standards, U.S. EPA
109 T.W. Alexander Drive, MD C504-02, RTP, NC 27711
(919) 541-3889 <a href="mailto:sasser.erika@epa.gov">sasser.erika@epa.gov</a>



From: Yamada, Richard (Yujiro) [yamada.richard@epa.gov]

**Sent**: 9/8/2017 2:04:42 PM

To: Beck, Nancy [Beck.Nancy@epa.gov]

**CC**: Dravis, Samantha [dravis.samantha@epa.gov]

Subject: Re: Formaldehyde - TIMELY

Samantha,

## Ex. 5 - Deliberative Process

Richard

Sent from my iPhone

On Sep 7, 2017, at 9:50 PM, Beck, Nancy < Beck.Nancy@epa.gov> wrote:

Samantha.

## Ex. 5 - Deliberative Process

Nancy.

Nancy B. Beck, Ph.D., DABT Deputy Assistant Administrator, OCSPP

P: 202-564-1273
M: Ex. 6 - Personal Privacy
Beck. Nancy@epa.gov

On Sep 7, 2017, at 9:39 PM, Dravis, Samantha <a href="mailto:dravis.samantha@epa.gov">dravis.samantha@epa.gov</a> wrote:

Nancy: Can you look into this?

Sent from my iPhone

Begin forwarded message:

From: "Newberry, Edward" <edward.newberry@squirepb.com>

**Date:** September 7, 2017 at 5:18:16 PM EDT

To: "dravis.samantha@epa.gov" <dravis.samantha@epa.gov>

Subject: Formaldehyde - TIMELY

Hi Sam,

I just received an urgent call from one of our clients, who manufactures, among other things, formaldehyde. They have been told that Tina Bahadori, Director of NCEA at EPA, (she a career employee who



assumed the director job this past January), has told people that she will release – as soon as next week – a toxicological assessment for formaldehyde. That assessment is expected to claim, based on a single small and flawed (flawed according to the National Academy of Sciences) study of Chinese workers that has been contradicted by other credible research, a link between formaldehyde and leukemia. According to the industry, the negative impacts of releasing such a study, particularly one that is contradicted by the weight of scientific evidence, are broad and enormous and this is the highest issue for the company. Other big companies like Georgia Pacific and others would be affected as well.

Senior management would like to meet with the Administrator as soon as possible – critical because they are told release of the report may come next week. Is that something that can be arranged? I am calling the Scott's office (I left a message for Millan) as well but wanted to give you a head's up and see if you could help. I am told that Ryan has been briefed on this and another colleague of mine is reaching out to him.

Hope you are well. I also wanted to follow up on the Potash Corporation issue we discussed a couple of weeks ago (summary below). Client (PCS) is eager to meet with you and the others as we discussed. Any chance we can get something set up for next week?

Thanks Sam.

Ed

#### Begin forwarded message:

From: "Newberry, Edward"

<edward.newberry@squirepb.com> **Date:** August 25, 2017 at 5:04:13 PM EDT

To: "dravis.samantha@epa.gov" <dravis.samantha@epa.gov>

Cc: "Winters, Karen A." <karen.winters@squirepb.com>,

"Jessica.DeMonte@potashcorp.com" < Jessica.DeMonte@potashcorp.com>

Subject: PotashCorp

Sam,

Thanks for talking with me earlier this week. We represent PotashCorp, the largest fertilizer company in the world producing potash, nitrogen and phosphate. Its subsidiary PCS Phosphate, has two phosphate mines in



the US, one of which is located in Aurora, North Carolina.

As we discussed, we'd like to come in and visit with you, Brittany and Mandy Gunasakara about a rule implemented during the Obama-era. See Phosphoric Manufacturing and Phosphate Fertilizer Production RTR and Standards of Performance for Phosphate Processing, 80 Fed. Reg. 50386 (August 19, 2015). The rule establishes mercury emissions limits for existing calciners (a calciner is a rotating steel cylinder used to heat and process the phosphate rock). The Aurora calciners are the only calciners in the country subject to the limit. The mercury limit is based on a statistically limited data set not representative of existing conditions. The limit also fails to take into account the variability of the mercury in the phosphate rock, which PCS Phosphate has no ability to control.

In setting the limit, US EPA determined that there was no adverse health risk associated with mercury emissions from the Aurora facility. EPA's Research Triangle Park office has expressed interest in working with PCS Phosphate to revise the limits, but has indicated they need direction from EPA headquarters.

The issue is critical because the projected cost of emissions controls may impact the viability of the facility, along with the jobs of its 850 employees and the hundreds of collateral businesses and jobs that support the facility and its operations. Moreover, controls are untested and may in fact prove not to be feasible.



North Carolina has already provided PCS Phosphate with what relief they can, however a new limit must be set and addressed through a rule revision on the federal level.

I would appreciate it if you were able to meet with me and my partner, Karen Winters, along with Jessica DeMonte, senior counsel for PCS. We are flexible on scheduling however anytime next Wednesday or Thursday or the week of September 11 would be best.

Thanks again. I look forward to seeing you.

Ed

\_\_\_\_\_

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#US



From: Kenneth A Mundt [kmundt@ramboll.com]

**Sent**: 10/3/2017 9:49:42 PM

**To**: Camacho, Iris [Camacho.Iris@epa.gov]

CC: jswenber@email.unc.edu; White, Kimberly [Kimberly\_White@americanchemistry.com]; Beck, Nancy

[Beck.Nancy@epa.gov]

Subject: RE: Invitation to Formaldehyde Expert Workshop at UNC

Dear Iris,

Wonderful! We welcome your participation. Indeed there is no registration fee.

I have cc'd Dr. Kimberly White of the ACC, and she will send you the participant's information package, including the agenda.

Please do not hesitate to contact Kimberly or me with any questions, and we very much look forward to seeing you in NC next week.

Yours sincerely

#### Kenneth A. Mundt, PhD, FACE

Health Sciences Practice Network Leader

D +1 413 835 4360 M +1 413 885 1345 kmundt@ramboll.com

Ramboll Environ 28 Amity Street Suite 2A Amherst, MA 01002 USA

www.ramboli-environ.com



From: Camacho, Iris [mailto:Camacho.Iris@epa.gov]

Sent: Tuesday, October 03, 2017 4:40 PM

To: Kenneth A Mundt

Cc: jswenber@email.unc.edu

Subject: RE: Invitation to Formaldehyde Expert Workshop at UNC

Hi Ken,

I will be attending the formaldehyde workshop. It is my understanding that you were notified that I will be the person representing EPA/OPPT (TSCA program).

I assume that no registration fees are required. I did not claim them in my travel authorization. I will appreciate a copy of the agenda.

Thanks.



李香香杂味水水素素多香香水水水水煮煮多香香水水水水煮煮多香水水水水煮煮多香水水水水煮煮多香水水水水煮煮多香水水水水煮煮煮煮水水水水煮煮多香香水水水水煮煮多香香

Iris A. Camacho, Ph.D.
Senior Science Advisor (on detail)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
William Jefferson Clinton Building East, 6308-A

Washington, DC 20460 Phone: 202-564-1229

Work hours: 8:00 am - 4:30 pm

Work cell phone: I Telework phone:

Ex. 6 - Personal Privacy

Email: camacho.iris@epa.gov

From: Kenneth A Mundt [mailto:kmundt@ramboll.com]

Sent: Wednesday, September 20, 2017 10:48 AM

To: Beck, Nancy < Beck. Nancy@epa.gov >

Cc: Swenberg, James A < jswenber@email.unc.edu>

Subject: Invitation to Formaldehyde Expert Workshop at UNC

Dear Dr. Beck,

Dr. Jim Swenberg and I are co-hosting an Invited Expert Workshop on the latest formaldehyde science and approaches to evidence integration, with an objective of identify the best path(s) forward for formaldehyde risk assessment. We are pleased to extend an invitation to you (please see attached invitation letter), and would be honored if you could join.

Please do not hesitate to contact me with any questions you may have. A full agenda for the meeting is close to being finalized, and I would be happy to share that with you as soon as it is.

Thank you for your consideration, and we hope to see you Chapel Hill.

Best,

Ken

Yours sincerely

Kenneth A. Mundt, PhD, FACE

Health Sciences Practice Network Leader



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#### Background

The 2011 NAS report of the EPA's draft IRIS assessment<sup>1</sup> recommended reviewing determinations of causality for specific lymphohematopoietic (LHP) cancers, and reviewing the criteria that were used to weigh evidence and assess causality. In the past 7 years, there have been numerous epidemiology studies, toxicology studies and mode of actions studies that clearly illustrate a lack of causal association between formaldehyde and leukemia. Those published and peer reviewed studies are summarized below.

Epidemiological Evidence which Shows Lack of Causal Association between Formaldehdye and Leukemia

- 1. Mundt, K., Gallagher, A., Dell, L., Natelson, E., Boffetta, P., and Gentry, R. Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells? (2017) Critical Reviews in Toxicology. Aug;47(7):592-602. Conducted additional and refined analysis on the key underlying data (including specifically exposure information which had not been previously provided) utilized in a study relied upon in the draft IRIS assessment (e.g. Zhang et al. 2010). The analysis evaluates exposed and unexposed populations and any potential correlations between formaldehyde exposure and aneuploidy among the exposed populations. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Additionally, among formaldehyde-exposed workers, no association was observed between individual formaldehyde exposure estimates and frequency of aneuploidy, which the original study authors suggested were indicators of myeloid leukemia risk.
- 2. Checkoway, H., Dell, L.D., Boffetta, P., Gallagher, A.E., Crawford, L., Lees, P.S., and Mundt, K.A. (2015). Formaldehyde exposure and mortality risks from acute myeloid leukemia and other Lymphohematopoietic Malignancies in the US National Cancer Institute cohort study of workers in Formaldehyde Industries. Journal of Occupational and Environmental Medicine, 57(7), 785-794. Authors obtained the data from the NCI cohort study via a Technology Transfer Agreement to replicate the findings reported by Beane Freemen et al. (2009) and to conduct additional analysis of associations of specific leukemias and lymphomas, especially acute myeloid leukemia, with formaldehyde exposure. Analyses were conducted including peak exposure as defined by Beane Freeman et al. (2009), as well as using an alternative more standard definition of peak exposure. The findings from this re-analysis fail to support the hypothesis that formaldehyde causes acute myeloid leukemia. Specifically, the results indicated: Acute myeloid leukemia was unrelated to "peak" or any other formaldehyde metric including the conventional cumulative exposure (also as reported in Beane Freeman (2009)). In fact, very few cohort members had any peak exposure within 20 years of death due to AML. There were suggestive associations with peak exposure only for chronic myeloid leukemia, albeit based on very small numbers. No other lymphohematopoietic malignancy was associated with either cumulative or peak exposure.
- 3. Coggon, D., Ntani, G., Harris, E. C., & Palmer, K. T. (2014). Upper airway cancer, myeloid leukemia, and other cancers in a cohort of British chemical workers exposed to formaldehyde. American Journal of Epidemiology, 179(11), 1301-1311. Conducted an update of mortality data through 2012 for the UK cohort of 14,008 formaldehyde users and producers and reported no increased mortality from myeloid leukemia (SMR 1.16, 95% CI 0.60 -2.20 for background exposure; SMR=1.46, 95% CI 0.84 2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450 -1.82 for

<sup>&</sup>lt;sup>1</sup> NAS 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. National Research Council. ISBN: 0-309-21194-8, 194 pages. Available at: <a href="http://www.nap.edu/catalog/13142.html">http://www.nap.edu/catalog/13142.html</a>.



EPA-18-0076-A-000349

high exposure). In a nested case-control analysis of 45 myeloid leukemias (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was increased (non-statistically significant) among workers exposed to high concentrations for < 1 year (OR=1.77, 95% CI 0.45 - 7.03), workers exposed to high concentrations  $\ge 1$  year showed no increased risk (OR 0.96, 95% CI 0.24 - 3.82)

- 4. Talibov, M., Lehtinen-Jacks, S., Martinsen, JI., Kjærheim, K., Lynge, E., Sparén, P., Tryggvadottir, L., Weiderpass, E., Kauppinen, T., Kyyrönen, P., Pukkala, E. (2014). Occupational exposure to solvents and acute myeloid leukemia: a population-based, casecontrol study in four Nordic countries Scandinavian Journal of Work, Environment & Hhealth 40.5: 511. Analyzed 15,332 newly diagnosed cases of AML (i.e., not deaths) diagnosed from 1961 to 2005 in Finland, Norway, Sweden, and Iceland, and 76,660 matched controls. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (HR 0.89, 95% CI 0.81 0.97 for workers exposed to ≤0.171 ppm-years; HR 0.92, 95% CI 0.83 -1.03 for workers exposed to 0.171 1.6 ppm-yrs, and HR=1.17, 95% CI 0.91 1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde).
- 5. Meyers, AR, Pinkerton, LE, Hein, MJ. (2013). Cohort mortality study of garment industry workers exposed to formaldehyde: Update and internal comparisons. AmJ IndMed 56(9):1027-39. Updated mortality data from 1960 through 2008 for 11,043 US garment workers employed at least three months between 1955 and 1983 at three US factories and exposed to formaldehyde. A total of 36 leukemia deaths were reported (SMR=1.04, 95% CI 0.73 1.44, compared to US mortality rates), of which 21 were myeloid leukemia (14 AML, 5 CML, 2 other and unspecified ML). The SMR for AML was 1.22 (95% CI 0.67 2.05), noting that "the extended follow-up did not strengthen previously observed associations."
- 6. Saberi Hosnijeh, F., Christopher, Y., Peeters, P., Romieu, I., Xun, W., Riboli, E., Raaschou-Nielsen, O., Tjønneland, A., Becker, N., Nieters, A., Trichopoulou, A., Bamia, C., Orfanos, P., Oddone, E., Luján-Barroso, L., Dorronsoro, M., Navarro, C., Barricarte, A., Molina-Montes, E., Wareham, N., Vineis, P., and Vermeulen, R. (2013). Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC)Occup Environ Med;70:464–470. Studied occupational risk factors among 671 incident leukemia cases (201 ML, including 113 AML, and 237 lymphoid leukemia) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy. Occupational exposures were estimated using a general population exposure matrix that classified occupational codes of study subjects into categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). No increased risk of AML was associated with low exposure to formaldehyde (HR 1.01, 95% CI 0.65 1.57) and no AML cases occurred among individuals in the high formaldehyde exposure category.

<u>Toxicological Evidence and Mode of Action Evidence which Shows Lack of Causal Association</u> between Formaldehdye and Leukemia

1. NTP Research Report on Absence of Formaldehyde-Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation Research Report 3, National Toxicology Program, August 2017. The full report can be found at: <a href="https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/formaldehyde">https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/formaldehyde</a> 508.pdf The objective

of the NTP study was to evaluate the potential role of the Trp53 gene in nasal carcinogenicity, leukemia or lymphohematopoietic cancer, and potentially other neoplasms in genetically susceptible mice. Male Trp53 haploinsufficient (Trp53+) mouse strains (B6.129-Trp53tm1Brd and C3B6.129F1-Trp53tm1Brd) were exposed via inhalation to 0 ppm, 7.5 ppm or 15 ppm formaldehyde for 8 weeks. Because evidence suggests a possible role of the Trp53 gene in formaldehyde-induced nasal squamous cell carcinomas, the authors hypothesized that formaldehyde-induced loss of Trp53 would result in an increase in susceptibility to formaldehyde-induced nasal squamous cell carcinoma, and possibly leukemia and other neoplasms. However, the study found that inhalation of a maximum tolerated dose of formaldehyde did not cause nasal tumors, an increased prevalence of leukemia or lymphohematopoietic cancer, or any other type of cancer in Trp53+ mice. The results from this study increase the weight of evidence that formaldehyde exposure is not causally associated with leukemia.

- 2. Albertini, R. J., & Kaden, D. A. (2016). Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?. Critical Reviews in Toxicology, 1-40. Research focused on the critical review and integration of the available peer-reviewed literature addressing the potential genotoxicity of formaldehyde. This publication also addresses the potential involvement of chromosome changes in blood cells suggested to be key events in proposed modes of action for the development of leukemia following formaldehyde exposure. The evaluation found reported genetic changes in circulating blood cells do not provide convincing support for formaldehyde classification as a human leukemogen. Specifically, the evaluation notes that no convincing evidence that exogenous exposures to formaldehyde alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect specifically not in the bone marrow. In addition, recent studies reporting changes in human bone marrow or hematopoietic precursor cells either have had confounding exposures or could not distinguish in vivo from in vitro occurrences.
- 3. Lai, Y., Yu, R., Hartwell, H. J., Moeller, B. C., Bodnar, W. M., & Swenberg, J. A. (2016). Measurement of Endogenous versus Exogenous Formaldehyde–Induced DNA-Protein Crosslinks in Animal Tissues by Stable Isotope Labeling and Ultrasensitive Mass Spectrometry. Cancer Research, 76(9), 2652-2661. Examined the formation, accumulation, and hydrolysis of DNA-protein crosslinks of both exogenous and endogenous formaldehyde. The results show that inhaled formaldehyde only reached rat and monkey noses, but not tissues distant to the site of initial contact.
- 4. Yu, R., Lai, Y., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., Bodnar, W., Starr, T., & Swenberg, J. A. (2015). Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. Toxicological Sciences, 146(1), 170-182. Evaluated the plausibility for inhaled formaldehyde to reach distal sites in rat and monkey models. The study indicated that inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact.
- 5. Edrissi, B., Taghizadeh, K., Moeller, B., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Dedon, P. (2013). Dosimetry of N 6-Formyllysine Adducts Following [13C2H2]-Formaldehyde Exposures in Rats. Chemical Research in Toxicology 26, no. 10: 1421-1423. The research found that Exogenous N6-formyllysine was detected in the nasal epithelium, but was not detected in the lung, liver, or bone marrow. Endogenous adducts dominated at all exposure conditions, The results parallel previous studies of formaldehyde-induced DNA adducts.



- 6. Rager, J., Moeller, B., Miller, S., Kracko, D., Doyle-Eisele, M., Swenberg, J., and Fry, R. (2014). Formaldehyde-associated changes in microRNAs: tissue and temporal specificity in the rat nose, white blood cells, and bone marrow. Toxicological Sciences: 138(1):36-46. doi:10.1093/toxsci/kft267. In this study, a multi-tiered approach was employed to enable an understanding of the genome-wide miRNA responses to formaldehyde and to establish how these responses relate to alterations in transcriptional profiles over time and in various tissues. This study found that formaldehyde inhalation exposure induces tissue and time-dependent responses at the genomic and epigenomic level. Formaldehyde exposure disrupts miRNA expression profiles within the rat nose and white blood cells but not within the bone marrow.
- 7. Rager, J., Moeller, B., Doyle-Eisele, M., Kracko, D., Swenberg, J., and Fry, R. (2013). Formaldehyde and epigenetic alterations: microRNA changes in the nasal epithelium of nonhuman primates." Environmental Health Perspectives (Online) 121, no. 3: 339. Research found that Formaldehyde exposure significantly disrupts miRNA expression profiles within the nasal epithelium. These results provide evidence for a relationship between formaldehyde exposure and altered signaling of the apoptotic machinery, likely regulated via epigenetic mechanisms.
- 8. Lu, K., Craft, S., Nakamura, J., Moeller, B., and Swenberg, J. (2012). Use of LC-MS/MS and stable isotopes to differentiate hydroxymethyl and methyl DNA adducts from formaldehyde and nitrosodimethylamine." Chemical Research in Toxicology 25, no. 3: 664-675. Research demonstrated that N(2)-hydroxymethyl-dG is the primary DNA adduct formed in cells following formaldehyde exposure. In addition, the study shows that alkylating agents induce methyl adducts at N(2)-dG and N(6)-dA positions, which are identical to the reduced forms of hydroxymethyl adducts arising from formaldehyde.
- 9. Moeller, B., Lu, K., Doyle-Eisele, M., McDonald, J., Gigliotti, A., and Swenberg, J. (2011). Determination of N 2-hydroxymethyl-dG adducts in the nasal epithelium and bone marrow of nonhuman primates following 13CD2-formaldehyde inhalation exposure. Chemical Research in Toxicology 24, no. 2: 162-164. Research found that both exogenous and endogenous adducts were readily detected and quantified in the nasal tissues of both exposure groups, with an exposure dependent increase in exogenous adducts observed. In contrast, only endogenous adducts were detectable in the bone marrow, even though ~10 times more DNA was analyzed.

Critical Reviews which Shows Lack of Causal Association between Formaldehdye and Leukemia

1. Mundt, K., Gentry, PR., Dell, L., Rodricks, J., and Boffetta, P. (2017). Six years after the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity. Regul Toxicol Pharmacol. 2017 Nov 20. pii: S0273-2300(17)30363-X. Evaluates the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. Indicated that overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of lymphohematopoietic malignancies (LHM) has increased substantially. The new evidence been published in each of the major streams of evidence (i.e., human, animal and mechanistic) consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the National Research Council (2011) scientific criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure.



- 2. Gentry, R., Rodricks, J., Turnbull, D., Bachand, A., Van Landingham, C., Shipp, A., Albertini, R., and Irons, R. (2013). Formaldehyde exposure and leukemia: Critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility. Critical Reviews in Toxicology 43, no. 8: 661-670. A critical review of the study, as well as a reanalysis of the underlying data, was performed and the results of this reanalysis suggested factors other than formaldehyde exposure may have contributed to the effects reported. Specifically, in the original study the authors did not follow their stated protocol and evaluation of the other study data indicates that the aneuploidy measured could not have arisen in vivo, but rather arose during in vitro culture. The results of the critical review and reanalysis of the data do not support a mechanism for a causal association between formaldehyde exposure and myeloid or lymphoid malignancies.
- 3. Swenberg, J., Moeller, B., Lu, K., Rager, J., Fry, R., and Starr, T. (2013). Formaldehyde Carcinogenicity Research 30 Years and Counting for Mode of Action, Epidemiology, and Cancer Risk Assessment. Toxicologic Pathology 41(2):181-189. doi:10.1177/0192623312466459. Article reviews the data for rodent and human carcinogenicity, early mode of action studies, more recent molecular studies of both endogenous and exogenous DNA adducts, and epigenetic studies. It goes on to demonstrate the power of these research studies to provide critical data to improve our ability to develop science-based cancer risk assessments, instead of default approaches.
- 4. Checkoway, H., Boffetta, P., Mundt, D., and Mundt, K. (2012). Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies." Cancer Causes & Control 23, no. 11: 1747-1766. Evaluation found that there is no consistent or strong epidemiologic evidence that formaldehyde is causally related to any of the lymphohematopoietic malignancies. Specifically, the evaluation noted that findings from occupational cohort and population-based case-control studies were very inconsistent for lymphohematopoietic malignancies, including myeloid leukemia. Apart from some isolated exceptions, relative risks were close to the null, and there was little evidence for dose-response relations for any of the lymphohematopoietic malignancies.



From: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]

**Sent**: 11/22/2017 2:07:55 PM

To: Fritz, Jason [Fritz.Jason@epa.gov]; Vulimiri, Suryanarayana [Vulimiri.Sury@epa.gov]; Bateson, Thomas

[Bateson.Thomas@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov];

Makris, Susan [Makris.Susan@epa.gov]; Segal, Deborah [Segal.Deborah@epa.gov]; Whalan, John

[Whalan.John@epa.gov]

CC: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Bussard, David [Bussard.David@epa.gov]

**Subject**: RE: Hot off the press - on formaldehyde

Ha ha. . . that's a good one, Jason. And of course, where else but RTP.

Ravi Subramaniam
RRB 51237/ (202) 564-2445 (o), Ex. 6 - Personal Privacy

From: Fritz, Jason

Sent: Wednesday, November 22, 2017 9:06 AM

**To:** Vulimiri, Suryanarayana <Vulimiri.Sury@epa.gov>; Bateson, Thomas <Bateson.Thomas@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Makris, Susan <Makris.Susan@epa.gov>; Segal, Deborah <Segal.Deborah@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Whalan, John <Whalan.John@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Bussard, David < Bussard. David@epa.gov>

Subject: RE: Hot off the press - on formaldehyde

Thanks Sury! It's a good time of year for turkey... jf

From: Vulimiri, Suryanarayana

Sent: Wednesday, November 22, 2017 8:27 AM

To: Bateson, Thomas <Bateson.Thomas@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Fritz, Jason <Fritz.Jason@epa.gov>; Kraft, Andrew@epa.gov>; Makris, Susan <Makris.Susan@epa.gov>; Segal, Deborah <Segal.Deborah@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Vulimiri, Suryanarayana <Vulimiri.Sury@epa.gov>; Whalan, John <Whalan.John@epa.gov>

Cc: Ramasamy, Santhini < <a href="mailto:Ramasamy.Santhini@epa.gov">Ramasamy, Santhini@epa.gov</a> Bussard, David <a href="mailto:Bussard.David@epa.gov">Bussard, David <a href="mailto:Bussard.David@epa.gov">Bussard.David@epa.gov</a> <a href="mailto:Bussard.David@epa.gov">Bussard.David@epa.gov</a> <a href="mailto:Bussard.Basid">Bussard.Basid</a> <a href="mailto:Bussard.Basid">Bussard.Basid</a> <a href="mailto:Bussard.Basid">Bussard.Basid</a> <a href="mailto:Basid</a> <a href="mailto:Basid</

**Subject:** Hot off the press - on formaldehyde

<< File: Mundt et al 2017\_Eupub.pdf >>

1. Regul Toxicol Pharmacol. 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

## Six years after the NRC Review of EPA's



EPA-18-0076-A-000354

# Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA1, Gentry PR2, Dell LD2, Rodricks JV2, Boffetta P3.

#### Author information:

- 1 Environment and Health, Ramboll Environ US Corporation, Amherst, MA, USA. Electronic address: kmundt@ramboll.com.
- 2 Environment and Health, Ramboll Environ US Corporation, Amherst, MA, USA. 3
- Icahn School of Medicine at Mount Sinai, New York, USA.

#### **Abstract**

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehyde causes leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011). They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

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**Sury Vulimiri, Ph.D., DABT** National Center for Environmental Assessment, Office of Research & Development, US EPA. Phone: 919-541-3558 | Fax: 919-541-0245 | vulimiri.sury@epa.gov



#### IRIS Ch

| Chemical                                 | CASRN      | RIS Assessment Lead |
|------------------------------------------|------------|---------------------|
| Ammonia- oral                            | 7664-41-7  | Vince Cogliano      |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
|                                          |            | Allen Davis         |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
|                                          |            | Allen Davis         |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
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| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
|                                          |            | Allen Davis         |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
|                                          |            | Allen Davis         |
|                                          |            |                     |
| Chloroform- inhalation                   | 67-66-3    | Ted Berner          |
| Chloroform- inhalation                   | 67-66-3    | Ted Berner          |
| Chloroform- inhalation                   | 67-66-3    | Ted Berner          |
| Chromium VI- inhalation                  | 18540-29-9 | Catherine Gibbons   |
|                                          |            | Alan Sasso          |
| Chromium VI- inhalation                  | 18540-29-9 | Catherine Gibbons   |
|                                          |            | Alan Sasso          |
| Chromium VI- inhalation                  | 18540-29-9 | Catherine Gibbons   |
|                                          |            | Alan Sasso          |
| ETBE- oral                               | 637-92-3   |                     |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Formaldehyde- oral                       | 50-00-0    | Barbara Glenn       |
|                                          |            | Andrew Kraft        |



### emical Patrons Information January 2018

| WC           |                   | Patron Contact Information |
|--------------|-------------------|----------------------------|
| JVV          | Greg Miller       | 202-566-2310               |
| ATSDR        | Selene Chou       | 770-488-3357               |
| FDA          | Suzie Fitzpatrick | 240-402-3042               |
|              |                   |                            |
| HealthCanada | Scott Blechinger  | 613-948-2018               |
| OAR          | Bob Hetes and     | 919-541-1589               |
|              | Deirdre Murphy    | 919-541-0729               |
| OLEM         | Stiven Foster and | 202-566-1911               |
|              | Kathleen Raffaele | 202-566-0301               |
| OP           | Dan Axelrad       | 202-566-2304               |
| OPP          | Garland Waleko    | 703-308-8049               |
| ЭW           | Greg Miller,      | 202-566-2310               |
|              | Tanja Crk,        | 202-566-1037               |
|              | Erica Fleisig,    | 202-566-1057               |
|              | John Healey       | 202-566-0176               |
| OAR          | Amy Vasu          | 919-541-0107               |
| OLEM         | Rich Kapuscinski  | 703-305-7411               |
| Region 4     | Glenn Adams       | 404-562-8771               |
| OW           | Greg Miller       | 202-566-2310               |
| Region 7     | Mike Beringer     | 913-551-7351               |
| Region 10    | Julie Wroble      | 206-553-1079               |
| OTAQ-OAR     | BEEN NO CONTACT   |                            |
| OAR          | Amy Vasu          | 919-541-0107               |
| OLEM         | Stiven Foster and | 202-566-1911               |
|              | Kathleen Raffaele | 202-566-0301               |
| OW           | Greg Miller       | 202-566-2310               |
| Region 1     | Meghan Cassidy    | 617-918-1387               |
| Region 2     | Marian Olsen      | 212-637-4313               |
| Region 4     | Glenn Adams       | 404-562-8771               |



| 17.0                                  |     |    |    |         |     |         |        |    |    |   |           |      |        |     |     |    |          |      |
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| Als                                   | n i | nt | ω. | · · · · | :+e | <br>• ( | <br>IE | D. | Δ  |   | <br><br>n | FE   | )<br>) | NIC | · r | )F |          |      |
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| Manganese- inhalation                                                                                                                    | 7439-96-5                                                                                               | Michael Wright                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Manganese- inhalation                                                                                                                    | 7439-96-5                                                                                               | Michael Wright                                                                                                                                     |
| Manganese- inhalation                                                                                                                    | 7439-96-5                                                                                               | Michael Wright                                                                                                                                     |
| Manganese- inhalation                                                                                                                    | 7439-96-5                                                                                               | Michael Wright                                                                                                                                     |
| МеНд                                                                                                                                     | 22967-92-6                                                                                              | Deb Segal                                                                                                                                          |
|                                                                                                                                          |                                                                                                         | Leonid Kopylev                                                                                                                                     |
| MeHg                                                                                                                                     | 22967-92-6                                                                                              | Deb Segal                                                                                                                                          |
|                                                                                                                                          |                                                                                                         | Leonid Kopylev                                                                                                                                     |
| МеНд                                                                                                                                     | 22967-92-6                                                                                              | Deb Segal                                                                                                                                          |
|                                                                                                                                          |                                                                                                         | Leonid Kopylev                                                                                                                                     |
| Mercury Salts                                                                                                                            |                                                                                                         | Jason Fritz                                                                                                                                        |
|                                                                                                                                          |                                                                                                         |                                                                                                                                                    |
| Naphthalene- oral and inhalation                                                                                                         | 91-20-3                                                                                                 | Ingrid Druwe                                                                                                                                       |
| Naphthalene- oral and inhalation                                                                                                         | 91-20-3                                                                                                 | Ingrid Druwe                                                                                                                                       |
| Naphthalene- oral and inhalation                                                                                                         | 91-20-3                                                                                                 | Ingrid Druwe                                                                                                                                       |
|                                                                                                                                          |                                                                                                         |                                                                                                                                                    |
| Naphthalene- oral and inhalation                                                                                                         | 91-20-3                                                                                                 | Ingrid Druwe                                                                                                                                       |
| Naphthalene- oral and inhalation                                                                                                         |                                                                                                         | Ingrid Druwe<br>Larissa Pardo                                                                                                                      |
|                                                                                                                                          | 14797-55-8                                                                                              |                                                                                                                                                    |
| Naphthalene- oral and inhalation                                                                                                         | 14797-55-8<br>14797-65-0                                                                                | Larissa Pardo                                                                                                                                      |
| Naphthalene- oral and inhalation<br>Nitrate/Nitrite- oral                                                                                | 14797-55-8<br>14797-65-0<br>14797-55-8                                                                  | Larissa Pardo<br>Xabier Arzuaga<br>Larissa Pardo                                                                                                   |
| Naphthalene- oral and inhalation<br>Nitrate/Nitrite- oral                                                                                | 14797-55-8<br>14797-65-0<br>14797-55-8                                                                  | Larissa Pardo<br>Xabier Arzuaga                                                                                                                    |
| Naphthalene- oral and inhalation  Nitrate/Nitrite- oral  Nitrate/Nitrite- oral                                                           | 14797-55-8<br>14797-65-0<br>14797-55-8                                                                  | Larissa Pardo<br>Xabier Arzuaga<br>Larissa Pardo<br>Xabier Arzuaga                                                                                 |
| Naphthalene- oral and inhalation  Nitrate/Nitrite- oral  Nitrate/Nitrite- oral                                                           | 14797-55-8<br>14797-65-0<br>14797-55-8                                                                  | Larissa Pardo<br>Xabier Arzuaga<br>Larissa Pardo<br>Xabier Arzuaga<br>Karen Hogan                                                                  |
| Naphthalene- oral and inhalation  Nitrate/Nitrite- oral  Nitrate/Nitrite- oral  PAH PRFs                                                 | 14797-55-8<br>14797-65-0<br>14797-55-8<br>14797-65-0                                                    | Larissa Pardo<br>Xabier Arzuaga<br>Larissa Pardo<br>Xabier Arzuaga<br>Karen Hogan<br>Ravi Subramaniam                                              |
| Naphthalene- oral and inhalation  Nitrate/Nitrite- oral  Nitrate/Nitrite- oral  PAH PRFs  PCBs- oral                                     | 14797-55-8<br>14797-65-0<br>14797-55-8<br>14797-65-0<br>1336-36-3                                       | Larissa Pardo Xabier Arzuaga Larissa Pardo Xabier Arzuaga Karen Hogan Ravi Subramaniam Geniece Lehmann                                             |
| Naphthalene- oral and inhalation  Nitrate/Nitrite- oral  Nitrate/Nitrite- oral  PAH PRFs  PCBs- oral  PCBs- oral                         | 14797-55-8<br>14797-65-0<br>14797-55-8<br>14797-65-0<br>1336-36-3<br>1336-36-3                          | Larissa Pardo Xabier Arzuaga Larissa Pardo Xabier Arzuaga Karen Hogan Ravi Subramaniam Geniece Lehmann Geniece Lehmann                             |
| Naphthalene- oral and inhalation  Nitrate/Nitrite- oral  Nitrate/Nitrite- oral  PAH PRFs  PCBs- oral  PCBs- oral  PCBs- oral             | 14797-55-8<br>14797-65-0<br>14797-55-8<br>14797-65-0<br>1336-36-3<br>1336-36-3<br>1336-36-3             | Larissa Pardo Xabier Arzuaga Larissa Pardo Xabier Arzuaga Karen Hogan Ravi Subramaniam Geniece Lehmann Geniece Lehmann Geniece Lehmann             |
| Naphthalene- oral and inhalation  Nitrate/Nitrite- oral  Nitrate/Nitrite- oral  PAH PRFs  PCBs- oral  PCBs- oral  PCBs- oral  PCBs- oral | 14797-55-8<br>14797-65-0<br>14797-55-8<br>14797-65-0<br>1336-36-3<br>1336-36-3<br>1336-36-3<br>121-82-4 | Larissa Pardo Xabier Arzuaga Larissa Pardo Xabier Arzuaga Karen Hogan Ravi Subramaniam Geniece Lehmann Geniece Lehmann Geniece Lehmann Lou D'Amico |



| OCHP         Sue Euling         202-566-2717           OLEM         Stiven Foster and Kathleen Raffaele         202-566-0301           Region 5         Carole Braverman         312-353-7359           OAR         Amy Vasu         919-541-0107           OCHP         Rebecca Dzubow and Sue Euling         202-566-2917           OW         Greg Miller         202-566-2310           OLEM         Stiven Foster Eathlee 202-566-2300           OAR         Amy Vasu         919-541-0107           OCHP         Sue Euling         202-566-2001           OAR         Amy Vasu         919-541-0107           OCHP         Sue Euling         202-566-0301           OLEM/Regional Superfund         Stiven Foster and 202-566-0301           Marlo Raffaele 202-566-0301         402-566-0301           Meghan Cassidy 617-918-1387         403-401           Marian Olsen 212-637-4313         312-886-2589           Kelly Schumacher 913-551-7963         913-551-7963           OPP Anna Lowit, 703-308-4135         Karen Hamernik, and CANNOT FIND 203-664-2532           OW         Greg Miller 202-566-2310           Region 5         Kimberely Harris 312-886-4239           OLEM         Marian Olsen 212-637-4313           Region 9 Patrick Wilson 415-972-3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | OAQPS-OAR                               | Amy Vasu         | 919-541-0107 |
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| OLEM         Stiven Foster and Kathleen Raffaele         202-566-1911           Region 5         Carole Braverman         312-353-7359           OAR         Amy Vasu         919-541-0107           OCHP         Rebecca Dzubow and Sue Euling         202-566-0967           OW         Greg Miller         202-566-2717           OW         Greg Miller         202-566-2310           OLEM         Stiven Foster         202-566-1911           Kathleen Raffaele         202-566-0301           OAR         Amy Vasu         919-541-0107           OCHP         Sue Euling         202-566-0301           OCHP         Sue Euling         202-566-0301           OLEM/Regional Superfund         Stiven Foster and 202-566-0301           Kathleen Raffaele 202-566-0301         413-918-1387           Marion Olsen 212-637-4313         212-637-4313           Marion Olsen 212-637-4313         212-637-4313           Marion Mangino 312-886-2589         201-564-5232           OW         Greg Miller         202-566-2310           Region 5         Kimberely Harris         312-886-4239           OLEM         Marian Olsen 212-637-4313           Region 9         Patrick Wilson 212-637-4313           Region 9         Patrick Wi                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | *************************************** |                  |              |
| Region 5         Carole Braverman         312-353-7359           OAR         Amy Vasu         919-541-0107           OCHP         Rebecca Dzubow         202-564-0967           and Sue Euling         202-566-2717           OW         Greg Miller         202-566-2310           OLEM         Stiven Foster         202-566-1911           Kathleen Raffaele         202-566-3001           OAR         Amy Vasu         919-541-0107           OCHP         Sue Euling         202-566-2717           OLEM/Regional Superfund         Stiven Foster and 202-566-0301           Marjan Cassidy         617-918-1387           Marian Olsen         212-637-4313           Marian Olsen         212-637-4313           Marian Olsen         212-637-4313           Marian Lowit,         703-308-4135           Karen Hamernik, and         CANNOT FIND           Susan Laessig         202-564-5232           OW         Greg Miller         202-566-2310           Region 5         Kimberely Harris         312-886-4239           OLEM         Marian Olsen         212-637-4313           Region 9         Patrick Wilson         415-972-3354           DOD           OAR         Bob Hete                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |                  |              |
| Region 5         Carole Braverman         312-353-7359           OAR         Amy Vasu         919-541-0107           OCHP         Rebecca Dzubow and Sue Euling         202-564-0967           OW         Greg Miller         202-566-2717           OW         Stiven Foster         202-566-2310           OLEM         Stiven Foster         202-566-0301           OAR         Amy Vasu         919-541-0107           OCHP         Sue Euling         202-566-2717           OLEM/Regional Superfund         Stiven Foster and 202-566-0301           Meghan Cassidy         617-918-1387           Marian Olsen         212-637-4313           Mario Mangino         312-886-2589           Kelly Schumacher         913-551-7963           OPP         Anna Lowit,         703-308-4135           Karen Hamernik, and         CANNOT FIND           Susan Laessig         202-564-5232           OW         Greg Miller         202-566-2310           Region 5         Kimberely Harris         312-886-4239           OLEM         Marian Olsen         212-637-4313           Region 9         Patrick Wilson         415-972-3354           DOD           OAR         Bob Hetes and         919                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |                  |              |
| OAR         Amy Vasu         919-541-0107           OCHP         Rebecca Dzubow and Sue Euling         202-564-0967           OW         Greg Miller         202-566-2717           OW         Stiven Foster 202-566-2310           OLEM         Stiven Foster 202-566-0301           OAR         Amy Vasu 919-541-0107           OCHP         Sue Euling 202-566-2717           OLEM/Regional Superfund Stiven Foster and Kathleen Raffaele 202-566-0301 Meghan Cassidy 617-918-1387 Marian Olsen 212-637-4313 Mario Mangino 312-886-2589 Melly Schumacher 913-551-7963           OPP         Anna Lowit, 703-308-4135 Karen Hamernik, and CANNOT FIND Susan Laessig 202-564-5232           OW         Greg Miller 202-566-2310           Region 5         Kimberely Harris 312-886-4239           OLEM         Marlene Berg 703-603-8701           Region 9 Patrick Wilson 415-972-3354           DOD           OAR         Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Region 5                                | Carole Braverman |              |
| OCHP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                         |                  |              |
| and Sue Euling       202-566-2717         OW       Greg Miller       202-566-2310         OLEM       Stiven Foster       202-566-1911         Kathleen Raffaele       202-566-0301         OAR       Amy Vasu       919-541-0107         OCHP       Sue Euling       202-566-2717         OLEM/Regional Superfund       Stiven Foster and 202-566-1911         Kathleen Raffaele 202-566-0301       Meghan Cassidy 617-918-1387         Marian Olsen 212-637-4313       Mario Mangino 312-886-2589         Kelly Schumacher 913-551-7963       913-551-7963         OPP       Anna Lowit, 703-308-4135         Karen Hamernik, and CANNOT FIND       Susan Laessig 202-564-5232         OW       Greg Miller 202-566-2310         Region 5       Kimberely Harris 312-886-4239         OLEM Marlene Berg 703-603-8701       Region 2 Marian Olsen 212-637-4313         Region 9 Patrick Wilson 415-972-3354       DOD         OAR       Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         | •                |              |
| OW       Greg Miller       202-566-2310         OLEM       Stiven Foster       202-566-1911         Kathleen Raffaele       202-566-0301         OAR       Amy Vasu       919-541-0107         OCHP       Sue Euling       202-566-2717         OLEM/Regional Superfund       Stiven Foster and 202-566-1911         Kathleen Raffaele 202-566-0301       Meghan Cassidy 617-918-1387         Marian Olsen 212-637-4313       Mario Mangino 312-886-2589         Kelly Schumacher 913-551-7963       913-551-7963         OPP       Anna Lowit, 703-308-4135         Karen Hamernik, and CANNOT FIND       Susan Laessig 202-564-5232         OW       Greg Miller 202-566-2310         Region 5       Kimberely Harris 312-886-4239         OLEM       Marlene Berg 703-603-8701         Region 2       Marian Olsen 212-637-4313         Region 9       Patrick Wilson 415-972-3354         DOD         OAR       Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | ОСНР                                    | Rebecca Dzubow   | 202-564-0967 |
| OLEM Stiven Foster 202-566-1911 Kathleen Raffaele 202-566-0301  OAR Amy Vasu 919-541-0107  OCHP Sue Euling 202-566-2717  OLEM/Regional Superfund Stiven Foster and 202-566-1911 Kathleen Raffaele 202-566-0301 Meghan Cassidy 617-918-1387 Marian Olsen 212-637-4313 Mario Mangino 312-886-2589 Kelly Schumacher 913-551-7963  OPP Anna Lowit, 703-308-4135 Karen Hamernik, and CANNOT FIND Susan Laessig 202-564-5232  OW Greg Miller 202-566-2310  Region 5 Kimberely Harris 312-886-4239  OLEM Marlene Berg 703-603-8701 Region 2 Marian Olsen 212-637-4313 Region 9 Patrick Wilson 415-972-3354  DOD  OAR Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                         | and Sue Euling   | 202-566-2717 |
| CATH LEARN ARTIFICIAL STATE OF THE PROOF OF THE                      | OW                                      | Greg Miller      | 202-566-2310 |
| CATH LEARN ARTIFICIAL STATE OF THE PROOF OF THE                      | OLEM                                    | Stiven Foster    | 202-566-1911 |
| OAR         Amy Vasu         919-541-0107           OCHP         Sue Euling         202-566-2717           OLEM/Regional Superfund         Stiven Foster and 202-566-0301 Kathleen Raffaele 202-566-0301 Meghan Cassidy 617-918-1387 Marian Olsen 212-637-4313 Mario Mangino 312-886-2589 Kelly Schumacher 913-551-7963           OPP         Anna Lowit, 703-308-4135 Karen Hamernik, and CANNOT FIND Susan Laessig 202-564-5232           OW         Greg Miller         202-566-2310           Region 5         Kimberely Harris         312-886-4239           OLEM         Marlene Berg         703-603-8701 Region 2 Region 2 Patrick Wilson 415-972-3354           DOD         DOD           OAR         Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | OLL III                                 |                  |              |
| OCHP         Sue Euling         202-566-2717           OLEM/Regional Superfund         Stiven Foster and Kathleen Raffaele         202-566-0301           Meghan Cassidy         617-918-1387           Marian Olsen         212-637-4313           Mario Mangino         312-886-2589           Kelly Schumacher         913-551-7963           OPP         Anna Lowit,         703-308-4135           Karen Hamernik, and Susan Laessig         202-564-5232           OW         Greg Miller         202-566-2310           Region 5         Kimberely Harris         312-886-4239           OLEM         Marlene Berg         703-603-8701           Region 2         Marian Olsen         212-637-4313           Region 9         Patrick Wilson         415-972-3354           DOD           OAR         Bob Hetes and         919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | OAR                                     |                  |              |
| OLEM/Regional Superfund         Stiven Foster and Kathleen Raffaele 202-566-1911         202-566-0301           Meghan Cassidy 617-918-1387         Marian Olsen 212-637-4313           Mario Mangino 312-886-2589         Mario Mangino 312-886-2589           Kelly Schumacher 913-551-7963         913-551-7963           OPP Anna Lowit, 703-308-4135         Karen Hamernik, and CANNOT FIND Susan Laessig 202-564-5232           OW         Greg Miller 202-566-2310           Region 5         Kimberely Harris 312-886-4239           OLEM Marlene Berg 703-603-8701         Region 2 Marian Olsen 212-637-4313           Region 9 Patrick Wilson 415-972-3354         DOD           OAR Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                  |              |
| Kathleen Raffaele   202-566-0301   Meghan Cassidy   617-918-1387   Marian Olsen   212-637-4313   Mario Mangino   312-886-2589   Kelly Schumacher   913-551-7963   OPP   Anna Lowit,   703-308-4135   Karen Hamernik, and   CANNOT FIND   Susan Laessig   202-564-5232   OW   Greg Miller   202-566-2310   OUT   CANNOT FIND   CANN |                                         |                  |              |
| Meghan Cassidy 617-918-1387 Marian Olsen 212-637-4313 Mario Mangino 312-886-2589 Kelly Schumacher 913-551-7963  OPP Anna Lowit, 703-308-4135 Karen Hamernik, and CANNOT FIND Susan Laessig 202-564-5232  OW Greg Miller 202-566-2310  Region 5 Kimberely Harris 312-886-4239  OLEM Marlene Berg 703-603-8701 Region 2 Marian Olsen 212-637-4313 Region 9 Patrick Wilson 415-972-3354  DOD  OAR Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                         |                  |              |
| Marian Olsen 212-637-4313 Mario Mangino 312-886-2589 Kelly Schumacher 913-551-7963  OPP Anna Lowit, 703-308-4135 Karen Hamernik, and CANNOT FIND Susan Laessig 202-564-5232  OW Greg Miller 202-566-2310  Region 5 Kimberely Harris 312-886-4239  OLEM Marlene Berg 703-603-8701 Region 2 Marian Olsen 212-637-4313 Region 9 Patrick Wilson 415-972-3354  DOD  OAR Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                         |                  |              |
| Mario Mangino 312-886-2589 Kelly Schumacher 913-551-7963 OPP Anna Lowit, 703-308-4135 Karen Hamernik, and CANNOT FIND Susan Laessig 202-564-5232 OW Greg Miller 202-566-2310  Region 5 Kimberely Harris 312-886-4239  OLEM Marlene Berg 703-603-8701 Region 2 Marian Olsen 212-637-4313 Region 9 Patrick Wilson 415-972-3354 DOD  OAR Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         | -                |              |
| OPP       Anna Lowit, 703-308-4135         Karen Hamernik, and Susan Laessig 202-564-5232       CANNOT FIND 202-566-2310         OW       Greg Miller 202-566-2310         Region 5       Kimberely Harris 312-886-4239         OLEM Marlene Berg 703-603-8701       Megion 2 Marian Olsen 212-637-4313         Region 9 Patrick Wilson 415-972-3354       DOD         OAR Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                         |                  |              |
| OPP       Anna Lowit, Karen Hamernik, and Susan Laessig       CANNOT FIND         Susan Laessig       202-564-5232         OW       Greg Miller       202-566-2310         Region 5       Kimberely Harris       312-886-4239         OLEM       Marlene Berg       703-603-8701         Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         | <del>-</del>     | 913-551-7963 |
| Karen Hamernik, and Susan Laessig       CANNOT FIND         OW       Greg Miller       202-564-5232         OW       Kimberely Harris       312-886-4239         OLEM       Marlene Berg       703-603-8701         Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | OPP                                     |                  |              |
| OW       Greg Miller       202-566-2310         Region 5       Kimberely Harris       312-886-4239         OLEM       Marlene Berg       703-603-8701         Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                         |                  | CANNOT FIND  |
| OW       Greg Miller       202-566-2310         Region 5       Kimberely Harris       312-886-4239         OLEM       Marlene Berg       703-603-8701         Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                         | Susan Laessig    | 202-564-5232 |
| OLEM       Marlene Berg       703-603-8701         Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | OW                                      |                  | 202-566-2310 |
| Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Region 5                                | Kimberely Harris | 312-886-4239 |
| Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                         |                  |              |
| Region 2       Marian Olsen       212-637-4313         Region 9       Patrick Wilson       415-972-3354         DOD         OAR       Bob Hetes and       919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | OLEM                                    | Marlene Berg     | 703-603-8701 |
| Region 9         Patrick Wilson         415-972-3354           DOD         OAR         Bob Hetes and         919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                         |                  |              |
| DOD           OAR         Bob Hetes and         919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                         |                  |              |
| OAR Bob Hetes and 919-541-1589                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                         |                  |              |
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| Deirdre Murphy 919-541-0729                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         | Deirdre Murphy   | 919-541-0729 |
| OW Greg Miller 202-566-2310                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | OW                                      |                  | 202-566-2310 |
| Region 10 Marc Stifelman 206-553-6979                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Region 10                               | Marc Stifelman   | 206-553-6979 |



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|         |           |         |        |       |      |  |



From: Bussard, David [Bussard.David@epa.gov]

**Sent**: 1/5/2018 4:22:33 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]

Subject: FYI: I passed ACC to Oregon materials to IO for coming up with Factsheet Q&As

From: Lehman, Rachel

Sent: Friday, January 05, 2018 10:16 AM

To: Bussard, David <Bussard.David@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>

Subject: RE: HCHO: for coming up with Factsheet Q&As

Thank you David! I am working on the soundbites/communications materials for formaldehyde. Thanks for passing this

along, it helps a lot!

Thanks again,

Rachel Lehman

Science Communications Associate (Contractor)

Human Health Risk Assessment Program

National Center of Environmental Assessment

Office of Research and Development, U.S. EPA

Lehman.Rachel@epa.gov

202-564-7179

From: Bussard, David

Sent: Friday, January 5, 2018 8:39 AM

To: D'Amico, Louis <DAmico.Louis@epa.gov>; Lehman, Rachel <lehman.rachel@epa.gov>

Subject: HCHO: for coming up with Factsheet Q&As

### Ex. 5 - Deliberative Process

I don't recall if Rachel was going to work on soundbites or someone else. Please pass along as appropriate.

David

From: Woodall, George

**Sent:** Thursday, January 04, 2018 3:36 PM **To:** Bussard, David < <u>Bussard</u>, David @epa.gov>

Subject: FW: HCHO

From: Bradfield, John

Sent: Thursday, January 04, 2018 3:19 PM



To: Woodall, George < Woodall. George@epa.gov>

Cc: Lavoie, Emma <Lavoie. Emma@epa.gov>; Vasu, Amy <Vasu. Amy@epa.gov>; Rimer, Kelly <Rimer. Kelly@epa.gov>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Dunkins, Robin

<<u>Ounkins.Robin@epa.gov</u>>; Hanks, Katie <<u>hanks.katie@epa.gov</u>>; Spence, Kelley <<u>Spence.Kelley@epa.gov</u>>; Hirtz, James <Hirtz.James@epa.gov>

Subject: RE: HCHO

Thanks, George. [

Ex. 5 - Deliberative Process

## Ex. 5 - Deliberative Process

It looks like our old friend formaldehyde is back, if it ever left.

John Bradfield

**Environmental Engineer** 

U.S. EPA I Natural Resources Group I Sector Policies and Programs Division, OAQPS 109 T.W. Alexander Drive (Mail Drop E143-03) I Research Triangle Park, NC 27711

Phone: 919.541.3062 | email: Bradfield.John@epa.gov

From: Woodall, George

Sent: Thursday, January 04, 2018 1:26 PM To: Bradfield, John <Bradfield.John@epa.gov>

Cc: Lavoie, Emma <Lavoie.Emma@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>;

Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Subject: RE: HCHO

John,

## Ex. 5 - Deliberative Process

At present, the IRIS assessment for formaldehyde remains in development. You can look at the IRIS web site for an update (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance nmbr=419&forceAssessmentTab=true). I have also copied the Assessment Managers - Barbara Glenn and Andrew Kraft - on this message in case they have more to offer or you would like to contact them directly with specific questions (no need for me to play middle man); however, feel free to cc: me on any correspondence.

I hope this helps Ex. 6 - Personal Privacy

George

George M. Woodall, PhD Toxicologist National Center for Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency



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Location: B231-D, EPA-RTP Main Campus

Office: (919) 541-3896 Mobile: Ex. 6 - Personal Privacy

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Postal Address: US EPA, MD B243-01, Research Triangle Park, NC 27711

Package Delivery: US EPA, MD B243-01, 4930 Old Page Road, Durham, NC 27703 Physical Address: US EPA, 109 TW Alexander Drive, Research Triangle Park, NC 27709

\*\*\*\*\*

From: Bradfield, John

**Sent:** Wednesday, January 03, 2018 3:17 PM **To:** Woodall, George < <u>Woodall, George@epa.gov</u>>

Subject: HCHO

George - As we head into the next heat on the PCWP RTR marathon, Industry is asking us about health benchmarks.

#### Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Is that accurate? If so, do you know who the ORD

Principle Investigator on formaldehyde is? Thanks.

John Bradfield

**Environmental Engineer** 

U.S. EPA I Natural Resources Group I Sector Policies and Programs Division, OAQPS 109 T.W. Alexander Drive (Mail Drop E143-03) I Research Triangle Park, NC 27711

Phone: 919.541.3062 | email: Bradfield John@epa.gov



From: Glenn, Barbara [Glenn.Barbara@epa.gov]

**Sent**: 1/3/2018 8:59:33 PM

To: D'Amico, Louis [DAmico.Louis@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]

Subject: RE: A favor s'il vou plait....

### Ex. 5 - Deliberative Process

From: D'Amico, Louis

Sent: Wednesday, January 03, 2018 3:42 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>

Subject: RE: A favor s'il vou plait....

## Ex. 5 - Deliberative Process

(NOTE NEW CONTACT

INFORMATION)

Louis D'Amico, Ph.D.

Assistant Center Director, Communications and Regulatory Support - National Center for Environmental Assessment Associate Director for Policy and Communications - Human Health Risk Assessment National Research Program U.S. EPA Office of Research and Development

damico.louis@epa.gov

O: (202) 564-4605 M: (Ex. 6 - Personal Privacy

From: Kraft, Andrew

Sent: Wednesday, January 3, 2018 3:36 PM

To: D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>

**Subject:** RE: A favor s'il vou plait....

NOOOOOOOOOOOOOOOO! He's going to ruin it!

From: D'Amico, Louis

Sent: Wednesday, January 03, 2018 3:34 PM

To: Glenn, Barbara < Glenn. Barbara@epa.gov >; Kraft, Andrew < Kraft. Andrew@epa.gov >

Subject: RE: A favor s'il vou plait....

Sadly, I am.... and sadly, I really do want it 🕾



Oops. Just got my approval email. Thank you!

-----

(NOTE NEW CONTACT

INFORMATION)

Louis D'Amico, Ph.D.

Assistant Center Director, Communications and Regulatory Support - National Center for Environmental Assessment Associate Director for Policy and Communications - Human Health Risk Assessment National Research Program

U.S. EPA Office of Research and Development

damico.louis@epa.gov

O: (202) 564-4605 M: Ex. 6 - Personal Privacy

From: Glenn, Barbara

Sent: Wednesday, January 3, 2018 3:33 PM

To: D'Amico, Louis <DAmico.Louis@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

**Subject:** RE: A favor s'il vou plait....

I don't think you are here. Are you real? Do you really want it? Okay.

From: D'Amico, Louis

Sent: Wednesday, January 03, 2018 3:31 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>

Subject: A favor s'il vou plait....

Any chance one of you can authorize my access to the IRIS formaldehyde assessment sharepoint site?

\_\_\_\_\_

(NOTE NEW CONTACT

INFORMATION)

Louis D'Amico, Ph.D.

Assistant Center Director, Communications and Regulatory Support (Acting)

National Center for Environmental Assessment

Associate Director for Policy and Communications

Human Health Risk Assessment National Research Program

U.S. EPA - Office of Research and Development

Mail Code 8601R | 1200 Pennsylvania Ave, NW | Washington, DC 20460

Office: 202-564-4605 | Mobile: Ex.6 - Personal Privacy email: damico.louis@epa.gov



From: Glenn, Barbara [Glenn.Barbara@epa.gov]

**Sent**: 9/8/2017 4:34:10 PM

To: Lavoie, Emma [Lavoie.Emma@epa.gov]

CC: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]

Subject: RE: Program and Regional Patron or Client engagement on IRIS assessments

Attachments: Formaldehyde\_Prog\_Region\_2017.docx

Hi Emma,

Attached is a descriptions of our EPA partners for formaldehyde and interactions in the last year.

Regards, Barbara and Andrew

From: Lavoie, Emma

Sent: Monday, August 28, 2017 10:03 AM

To: Davis, Allen <Davis.Allen@epa.gov>; Lee, Janice <Lee.JaniceS@epa.gov>; Gibbons, Catherine

<Gibbons.Catherine@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Arzuaga, Xabier <Arzuaga.Xabier@epa.gov>;

Weaver, Andre <Weaver.James@epa.gov>; Yost, Erin <Yost.Erin@epa.gov>; Keshava, Nagalakshmi

<Keshava.Nagu@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Segal,

Deborah <Segal.Deborah@epa.gov>; Keshava, Channa <Keshava.Channa@epa.gov>; Druwe, Ingrid

<Druwe.lngrid@epa.gov>; Li, Jenny <Li.Jenny@epa.gov>; Pardo, Larissa <Pardo.Larissa@epa.gov>; Hogan, Karen

< Hogan. Karen@epa.gov>; Pratt, Margaret < pratt.margaret@epa.gov>; Carlson, Laura < Carlson. Laura@epa.gov>; Carlson, Laura@epa.gov>; Carlson, Laura@epa.gov>; Carlson, Laura@epa.gov>; Carlson, Laura@epa.gov>; Carlson, Laura@epa.gov>; Carlson, Laura < Carlson, Laura@epa.gov>; Carlson, Laura

Lehmann, Geniece < Lehmann. Geniece@epa.gov>

**Cc:** Thayer, Kris <thayer.kris@epa.gov>; Avery, James <Avery.James@epa.gov>; Fritz, Jason <Fritz.Jason@epa.gov>;

Soto, Vicki <Soto.Vicki@epa.gov>

Subject: Program and Regional Patron or Client engagement on IRIS assessments

IRIS assessment managers:

I'd like to check-in with you about who and how often you are engaging your clients/partners/patrons in the program and regional offices.

Please reply to me with the following information (briefly):

Who do you consider your 'patron' or 'client' in the Programs and/or Regions?

How often do you interact with them e.g., give updates, answer questions or give presentations? How often in the last 12 months?

I'll use this information to work with you to improve or refine our interactions as assessments move forward.

I have worked with some of you in the last year on Patron/client interactions but may not have discussed this much in the last few months. If an assessment manager is missing from this email, it is because I have recent activity with them regarding their Patrons or their assessment is in SAB review.

For phthalates, Erin Yost has started this conversation with me, but if you have anything specific on any part of the phthalates work, please still share it.

Otherwise I'm specifically interested in these assessments:

Arsenic inorg

**BBP** 

Chromium VI

DBP

DEP

DIBP



DINP
Formaldehyde
Naphthalene
Nitrate Nitrite
PAH RPFs
PCBs
tert-Butanol

-Emma

Emma T. Lavoie, PhD
Assistant Center Director for Scientific Support
National Center for Environmental Assessment
US Environmental Protection Agency

Tel: 703-347-0328



From: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]

**Sent**: 2/7/2018 3:18:13 PM

**To**: Kraft, Andrew [Kraft.Andrew@epa.gov]

CC: Glenn, Barbara [Glenn.Barbara@epa.gov]; Bussard, David [Bussard.David@epa.gov]

**Subject**: RE: follow up on HCHO

Attachments: 2018-02-06 Overview Internal Factsheet - bullet version\_TB.docx

Hi Andrew,

# Ex. 5 - Deliberative Process



# Ex. 5 - Deliberative Process

From: Bussard, David

Sent: Wednesday, February 07, 2018 10:00 AM

To: Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>

Subject: RE: follow up on HCHO

## Ex. 5 - Deliberative Process

#### David

From: Ramasamy, Santhini

**Sent:** Wednesday, February 07, 2018 8:04 AM **To:** Kraft, Andrew < <u>Kraft.Andrew@epa.gov</u>>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov>

Subject: RE: follow up on HCHO

Thank you Andrew for pointing me out the information. While I was looking through the materials in a hurry, I missed this info. I knew you had it somewhere. I was trying to find this from Tox Review.

From: Kraft, Andrew

Sent: Wednesday, February 07, 2018 7:56 AM

To: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov>

Subject: Re: follow up on HCHO

The slide I was referring to is slide 26 in the attached deck, although there may be some other useful tidbits to extract from these slides.

-Andrew

From: Ramasamy, Santhini

Sent: Wednesday, February 7, 2018 7:53 AM

To: Kraft, Andrew



**Cc:** Glenn, Barbara; Bussard, David **Subject:** RE: follow up on HCHO

Hi Andrew,

Tina has not gotten back to us. There may be need for additional information. One question regarding the IUR and RfC comparison. Can you send me that info presented to Bob K?

Santhini

From: Kraft, Andrew

Sent: Wednesday, February 07, 2018 7:48 AM

To: Bussard, David < Bussard. David@epa.gov >; Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >

Cc: Glenn, Barbara < Glenn.Barbara@epa.gov>

Subject: Re: follow up on HCHO

### Ex. 5 - Deliberative Process

-Andrew

From: Bussard, David

**Sent:** Tuesday, February 6, 2018 4:21 PM **To:** Ramasamy, Santhini; Lehman, Rachel

Cc: D'Amico, Louis; Kraft, Andrew; Glenn, Barbara; Champlin, Anna

Subject: RE: follow up on HCHO

I filled in some of the blanks. I did in track changes to we can see what changed.

David

From: Ramasamy, Santhini

**Sent:** Tuesday, February 06, 2018 4:03 PM **To:** Lehman, Rachel < lehman.rachel@epa.gov >

**Cc:** D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Champlin, Anna

<Champlin.Anna@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: FW: follow up on HCHO

Hi Rachel,

Please see attached formaldehyde briefing materials for Ryan Jackson. David submitted this version to Tina and Kris this afternoon. You may wait until we get Tina and Kris's feedback.



Thanks.

Santhini

From: Bahadori, Tina

Sent: Tuesday, February 06, 2018 7:41 AM

To: Ross, Mary <Ross.Mary@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Thayer, Kris

<<u>thayer.kris@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>

**Cc:** Champlin, Anna < <u>Champlin.Anna@epa.gov</u>>; D'Amico, Louis < <u>DAmico.Louis@epa.gov</u>>

Subject: Fwd: follow up on HCHO

Shall we? Barbara and Andrew, are you willing to take a first stab at drafting this?

Τ.

Begin forwarded message:

From: "Orme-Zavaleta, Jennifer" <Orme-Zavaleta.Jennifer@epa.gov>

**Date:** February 6, 2018 at 7:27:30 AM EST

To: "Bahadori, Tina" < Bahadori. Tina@epa.gov>

**Cc:** "Robbins, Chris" < <u>Robbins.Chris@epa.gov</u>>, "Christian, Megan"

<<u>Christian.Megan@epa.gov</u>>
Subject: follow up on HCHO

#### Ex. 5 - Deliberative Process

Does not have to be a comparison to what ACC claims

Thanks!

Jennifer Orme-Zavaleta, PhD Principal Deputy Assistant Administrator for Science USEPA Office of Research and Development

D(
RT Ex. 6 - Personal Privacy
91
orme-zavaleta.jennifer@epa.gov



From: D'Amico, Louis [DAmico.Louis@epa.gov]

**Sent**: 10/10/2017 3:13:57 PM

To: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Rieth, Susan

[Rieth.Susan@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]

CC: Bussard, David [Bussard.David@epa.gov]; Rutigliano, Marian [Rutigliano.Marian@epa.gov]; Jones, Samantha

[Jones.Samantha@epa.gov]

Subject: RE: Michigan question re formaldehyde

(+ Samantha)

In general, I think we should respond to the question that's being asked, which is specifically:

Is it likely the final revised or final assessment will be out in 2018?

#### Ex. 5 - Deliberative Process

Are you likely changing the MMOA mechanism?

#### Ex. 5 - Deliberative Process

I've never seen the Preuss memos, and in general don't think they would convey the same authority as the actual assessments (or peer reviewed journal articles)?

If the team wants to work up answers to the questions, I'm happy to review prior to response.

Louis D'Amico, Ph.D.

Assistant Center Director for Communications and Regulatory Support (Acting)

U.S. EPA, ORD/NCEA

damico.louis@epa.gov

O: (703) 347-0344 N Ex. 6 - Personal Privacy

From: Subramaniam, Ravi

Sent: Tuesday, October 10, 2017 9:55 AM

To: Glenn, Barbara <Glenn.Barbara@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Rieth, Susan

<Rieth.Susan@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Cc: Bussard, David <Bussard.David@epa.gov>; Rutigliano, Marian <Rutigliano.Marian@epa.gov>

**Subject:** RE: Michigan question re formaldehyde

## Ex. 5 - Deliberative Process



Ravi.

Ravi Subramaniam
PYS 11782/ (703) 347-8606 (o), 1 Ex. 6 - Personal Privacy

From: Glenn, Barbara

Sent: Tuesday, October 10, 2017 9:30 AM

To: D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Rieth, Susan <<u>Rieth.Susan@epa.gov</u>>; Kraft, Andrew

<Kraft.Andrew@epa.gov>

Cc: Subramaniam, Ravi < Subramaniam.Ravi@epa.gov>; Bussard, David < Bussard.David@epa.gov>; Rutigliano, Marian

<Rutigliano.Marian@epa.gov>

Subject: RE: Michigan question re formaldehyde

Hey Lou,

I agree this is a question about formaldehyde schedule. We have another request regarding our schedule that we have not as yet answered. So deciding what that answer is would be really good.

Regards, Barbara

From: D'Amico, Louis

**Sent:** Friday, October 06, 2017 1:26 PM **To:** Rieth, Susan <a href="mailto:Rieth.Susan@epa.gov">Rieth.Susan@epa.gov</a>

Cc: Subramaniam, Ravi < Subramaniam.Ravi@epa.gov >; Bussard, David < Bussard.David@epa.gov >; Glenn, Barbara

<<u>Glenn.Barbara@epa.gov</u>>; Rutigliano, Marian <<u>Rutigliano.Marian@epa.gov</u>>

Subject: Re: Michigan question re formaldehyde

Let's touch base on this on Tuesday. The question isn't about historical actions by epa, but the timing of any activity about formaldehyde. Not sure I see the point of sending them copies of older memos.

Lou

(703) 347-0344 (o)

Ex. 6 - Personal Privacy

Sent from my iPhone

(Please pardon brevity and typos)

On Oct 6, 2017, at 12:11 PM, Rieth, Susan < Rieth.Susan@epa.gov > wrote:

Hi Ravi.

FYI, I also forwarded to David, Andrew, and Barbara. Sue

----Original Message----

From: Subramaniam, Ravi

Sent: Friday, October 06, 2017 12:08 PM

To: D'Amico, Louis < DAmico.Louis@epa.gov>

Cc: Bussard, David <<u>Bussard.David@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Rutigliano, Marian <<u>Rutigliano.Marian@epa.gov</u>>; Rieth, Susan <<u>Rieth.Susan@epa.gov</u>>

Subject: Michigan question re formaldehyde

Lou:

Marian brought this communication (through the Hotline) from Michigan state to my attention. It



would be useful to send them the Preuss memos (2007, 2010) which served as the basis for some program office actions. I am thinking there were two of them but I need to check.

Ravi.

Ravi Subramaniam

PYS 11782/ (703) 347-8606 (o), 1 Ex. 6 - Personal Privacy

----Original Message-----From: Rutigliano, Marian

Sent: Friday, October 06, 2017 11:25 AM

To: Subramaniam, Ravi < Subramaniam. Ravi@epa.gov>

Subject: FW: Form submission from: IRIS Contact us about the Integrated Risk Information

System form

----Original Message----

From: King, Bernard

Sent: Friday, October 06, 2017 11:22 AM

To: Radke-Farabaugh, Elizabeth < radke-farabaugh elizabeth@epa.gov >; Rieth, Susan

<<u>Rieth.Susan@epa.gov</u>>; Rutigliano, Marian <<u>Rutigliano.Marian@epa.gov</u>>; Pratt, Margaret

cyratt.margaret@epa.gov; D'Amico, Louis CDAmico.Louis@epa.gov; Soto, Vicki

<Soto.Vicki@epa.gov>

Cc: Semeniuk, Michael < Semeniuk Michael @epa.gov>

Subject: FW: Form submission from: IRIS Contact us about the Integrated Risk Information

System form

**FYI** 

Thank you for contacting the IRIS Hotline.

Sincerely,

Bernard King

IRIS Hotline EPA Docket Center

Records Information Manager III

Records information Manager III

Artic Slope Mission Services (ASMS) - Contractor

Phone: (202) 566-1676

Email: king.bernard@epa.gov

----Original Message----

From: drupal admin [mailto:drupal admin@epa.gov]

Sent: Friday, October 06, 2017 11:10 AM

To: IRIS HOTLINE < IRIS HOTLINE@epa.gov>

Subject: Form submission from: IRIS Contact us about the Integrated Risk Information System

form



Submitted on 10/06/2017 11:09AM Submitted values are:

Name: Dr Divinia Ries Email: riesd@michigan.gov

Comments: We are updating the Michigan cleanup criteria for formaldehyde and initially proposed the use of 2010 IRIS draft's IURF value and the recommendation for mutagenic MOA classification. Due to stakeholder comment, we are now proposing the IRIS 1991 IURF value but retained the MMOA application. Question - Is it likely the final revised or final assessment will be out in 2018? Are you likely changing the MMOA mechanism? Thanks!

Web Area: IRIS



From: Bussard, David [Bussard.David@epa.gov]

**Sent**: 10/6/2017 8:10:15 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Glenn, Barbara

[Glenn.Barbara@epa.gov]

**Subject**: RE: Next Steps on Formaldehyde - updated schedule

## Ex. 5 - Deliberative Process

#### David

From: Kraft, Andrew

**Sent:** Friday, October 06, 2017 3:42 PM

To: Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Glenn,

Barbara <Glenn.Barbara@epa.gov>

Subject: Re: Next Steps on Formaldehyde - updated schedule

### Ex. 5 - Deliberative Process



### Ex. 5 - Deliberative Process

-Andrew

From: Bussard, David

Sent: Friday, October 6, 2017 3:22 PM

**To:** Ramasamy, Santhini; Kraft, Andrew; Glenn, Barbara **Subject:** FW: Next Steps on Formaldehyde - updated schedule

#### Ex. 5 - Deliberative Process

David

From: Bahadori, Tina

Sent: Friday, October 06, 2017 2:40 PM

To: Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara

<Glenn.Barbara@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy.Santhini@epa.gov >; Shams, Dahnish < Shams.Dahnish@epa.gov >; Jones,

Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>;

Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

### Ex. 5 - Deliberative Process

Thanks again for being so very great – all of you.

Tina

From: Soto, Vicki

Sent: Thursday, October 5, 2017 8:20 AM

**To:** Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov</a>>; Glenn, Barbara < <a href="mailto:Glenn.Barbara@epa.gov">Glenn, Barbara@epa.gov</a>>; Bahadori, Tina@epa.gov</a>>

**Cc:** Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Shams, Dahnish <<u>Shams, Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones, Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico, Louis@epa.gov</u>>; Ross, Mary



<<u>Ross.Mary@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>;

Thayer, Kris <thayer.kris@epa.gov>

**Subject:** RE: Next Steps on Formaldehyde - updated schedule

#### Ex. 5 - Deliberative Process

From: Kraft, Andrew

Sent: Thursday, October 05, 2017 8:13 AM

**To:** Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Shams, Dahnish < Shams. Dahnish@epa.gov>; Jones,

Samantha < <u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis < <u>DAmico.Louis@epa.gov</u>>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>;

Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

### Ex. 5 - Deliberative Process

Patiently,

Andrew and (speaking for) Barbara

From: Soto, Vicki

Sent: Wednesday, October 04, 2017 8:03 PM

**To:** Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Bahadori, Tina <<u>Bahadori,Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>

Cc: Ramasamy, Santhini <Ramasamy, Santhini@epa.gov>; Shams, Dahnish <Shams, Dahnish@epa.gov>; Jones,

Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>; Ross, Mary

<Ross.Mary@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>;

Thayer, Kris < thayer.kris@epa.gov>

**Subject:** RE: Next Steps on Formaldehyde - updated schedule

#### Hi everyone,

I tried to take the bullets below and wrap them into the schedule of Formaldehyde in Project. I've thrown in some highlighting to pull attention to some of those dates. I think it seems really tight. The lines that are 0 duration are milestones (for reports-most of them are a brown color) and can be ignored. This can always be altered if it doesn't make sense.

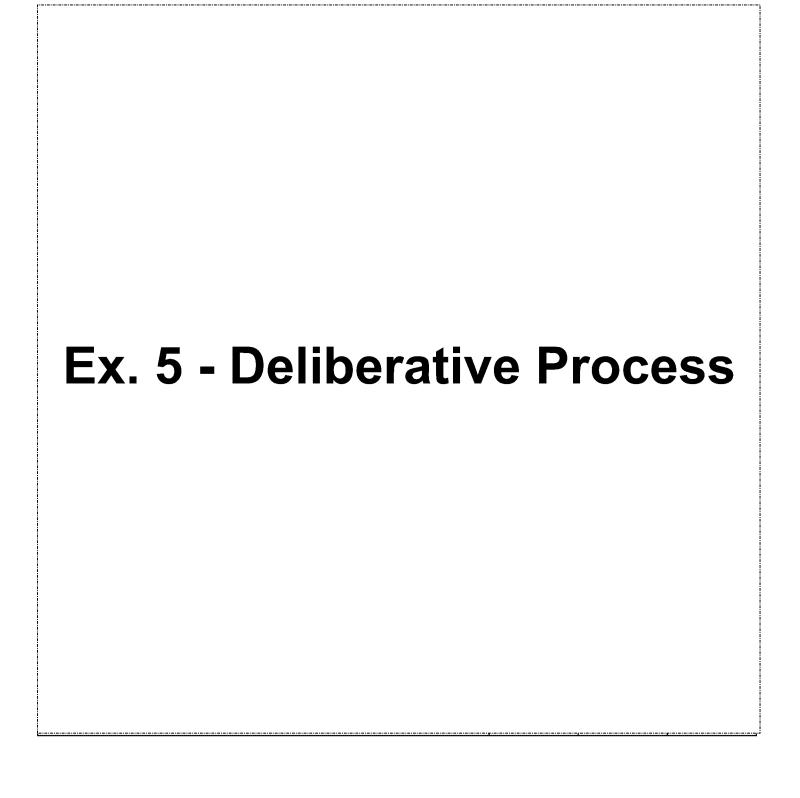
Vicki

### Ex. 5 - Deliberative Process



# Ex. 5 - Deliberative Process





From: Glenn, Barbara

Sent: Thursday, September 28, 2017 11:24 AM

To: Bahadori, Tina <a href="mailto:Kraft">Bahadori</a>. Tina@epa.gov</a>; Kraft, Andrew <a href="mailto:Kraft">Kraft</a>. Andrew@epa.gov</a>; Bussard, David
<a href="mailto:Bussard,David@epa.gov">Bussard, David
<a href="mailto:Bussard,David@epa.gov">Bussard,David
<a href="mailto:Bussard,David@epa.gov">Bussard,David
<a href="mailto:Bussard,David@epa.gov">Bussard,David
<a href="mailto:Bussard,David@epa.gov">Bussard,David
<a href="mailto:Bussard,David@epa.gov">Bussard,David
<a href="mailto:Bussard,Basid
Bussard,David@epa.gov">Bussard,David
Bussard,David
Bussard,Basid
Bussard,Bas



Subject: RE: Next Steps on Formaldehyde

Hi Tina,

### Ex. 5 - Deliberative Process

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 11:10 AM

**To:** Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Bussard, David < Bussard. David@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Lavoie, Emma < Lavoie. Emma@epa.gov > Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >; Soto, Vicki < Soto. Vicki@epa.gov >; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Thanks Andrew. So, with this timeline, can we punctuate the rest of the timeline?

### Ex. 5 - Deliberative Process

Tina

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 10:35 AM

To: Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Glenn, Barbara <<u>Glenn, Barbara@epa.gov</u>>; Bussard, David <<u>Bussard, David@epa.gov</u>>; Thayer, Kris <<u>thayer, kris@epa.gov</u>>; Lavoie, Emma <<u>Lavoie, Emma@epa.gov</u>>
Cc: Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto, Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams, Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones, Samantha@epa.gov</u>>; D'Amico, Louis <<u>OAmico, Louis@epa.gov</u>>; Ross, Mary <<u>Ross, Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

Hi Tina,

## Ex. 5 - Deliberative Process



### Ex. 5 - Deliberative Process

-Barbara and Andrew

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:05 PM

To: Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>
Cc: Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

### Ex. 5 - Deliberative Process

T.

From: Glenn, Barbara

Sent: Tuesday, September 26, 2017 9:03 AM

To: Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft, Andrew@epa.gov</u>>; Bussard, David <<u>Bussard, David@epa.gov</u>>; Thayer, Kris <<u>thayer, kris@epa.gov</u>>; Lavoie, Emma <<u>Lavoie, Emma@epa.gov</u>> Cc: Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto, Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams, Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones, Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico, Louis@epa.gov</u>>; Ross, Mary <<u>Ross, Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

Hello Tina.

### Ex. 5 - Deliberative Process

Thanks, Andrew and Barbara

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 8:27 AM

To: Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>
Cc: Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: FW: Next Steps on Formaldehyde



### Ex. 5 - Deliberative Process

Other thoughts?

T.

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>

Cc: Kavlock, Robert < Kavlock. Robert@epa.gov >; Rodan, Bruce < rodan.bruce@epa.gov >; Orme-Zavaleta, Jennifer

<<u>Orme-ZavaletaJennifer@epa.gov</u>>; Gwinn, Maureen <<u>gwinn.maureen@epa.gov</u>>; Sjogren, Mya

<<u>Sjogren.Mya@epa.gov</u>>; Kuhn, Kevin <<u>Kuhn.Kevin@epa.gov</u>>; Fegley, Robert <<u>Fegley.Robert@epa.gov</u>>; Ross,

Mary <<u>Ross.Mary@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Bussard, David <Bussard.David@epa.gov>

Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday — I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices — Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile: 1Ex-6-Personal Privacy 1; Email: Bahadorí Tina@epa.gov



From: Thayer, Kris [thayer.kris@epa.gov]

**Sent**: 11/22/2017 3:37:34 PM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Bussard, David

[Bussard.David@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

My calendar is up to date, I'm on leave Dec 20-Jan 4 but could do Dec 21 or 22 (not 20th since I'll be in the air)

From: Lidka Maslankiewicz [mailto:lidka.maslankiewicz@rivm.nl]

**Sent:** Wednesday, November 22, 2017 10:33 AM **To:** Glenn, Barbara < Glenn.Barbara@epa.gov>

**Cc:** Bussard, David <Bussard.David@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Els Smit <els.smit@rivm.nl>;

Joke Herremans <joke.herremans@rivm.nl>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Paul Janssen <paul.janssen@rivm.nl>; Thayer, Kris <thayer.kris@epa.gov>; Theo Vermeire <theo.vermeire@rivm.nl> Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Barbara and Andrew,

It is our turn to apologize for a delay.

Yes, we would be very interested to talk about the formaldehyde assessment and its methods for quantification of cancer risk for NPC. As I have already informed you, we are currently in the process of updating our national air limit for this chemical and we would like to use the data as presented in the 2010 draft, more specifically the quantification of cancer risks for NPC (Nasopharyngeal Cancer), based either on human data and on animal data as presented in this Draft.

We would appreciate the opportunity to discuss the current status of the IRIS Toxicological Review of Formaldehyde.

We are also interested if there is any possibility to use the data (especially derived inhalation cancer unit risk for NPC (Nasopharyngeal Cancer)), without referring as to an official EPA position, but rather a scientific approach.

We have noted that in 2014 US-EPA convened a workshop

(https://www.epa.gov/sites/production/files/2014-

12/documents/formaldehyde workshop agenda final.pdf), the topics of which were the endogenous formation of formaldehyde and its relation to formaldehyde toxicity and the mechanistic evidence for lymphohematopoietic cancer induction by formaldehyde. Any further information on these topics and on the envisaged timeline for finalization of the US-EPA IRIS evaluation would be very welcome.

We also would like to know, how will US-EPA react to the comments of NAS (especially their comments on the calculation of the unit risks)? Moreover, will the unit risk calculation change in the near future?

Here are several dates we would like to propose:

13th, 20th, 21st or 22nd of December 2017, 9 - 10 am EST (15:00 - 16:00 our time), or

 $17^{th}$ ,  $18^{th}$ ,  $24^{th}$  or  $25^{th}$  of January 2018, 9-10 am EST (15:00 – 16:00 our time).

We hope to hear from you soon.

Kind regards



#### Lidka

Lidka Maslankiewicz National Institute for Public Health and the Environment (RIVM) Centre for Safety of Substances and Products tel. 31 (0)30 2743160 +31 6 46 86 07 73

e-mail: Lidka.Maslankiewicz@rivm.nl

From: "Glenn, Barbara" < Glenn.Barbara@epa.gov >

To: Lidka Maslankiewicz <a href="mailto:lidka.maslankiewicz@rivm.nl">lidka Maslankiewicz <a href="mailto:lidka.maslankiewicz@rivm.nl">lidka.maslankiewicz@rivm.nl</a>, "Kraft, Andrew" <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov</a>,

Cc: "Bussard, David" <<u>Bussard.David@epa.gov</u>>, "D'Amico, Louis" <<u>DAmico.Louis@epa.gov</u>>, Els Smit <<u>els.smit@rivm.nl</u>>, Joke Herremans <<u>joke.herremans@rivm.nl</u>>, Paul Janssen <<u>paul.janssen@rivm.nl</u>>, "Thayer, Kris" <<u>thayer.kris@epa.gov</u>>, Theo Vermeire <<u>theo.vermeire@rivm.nl</u>>

Date: 10/10/2017 04:48 PM

fax. 31 (0)30 2744401

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Lidka,

We would like to schedule a time to talk about the formaldehyde assessment and its methods for quantification of cancer risk for NPC. It would be great to explore what might be possible. I have some proposed dates and times for you to select from. Will this be possible for you?

Oct. 30 9 – 10 am EST Nov 1 9 – 10 am EST Nov 7 9 – 10 am EST

Thank you very much for your patience with our process and timing. Regards, Barbara and Andrew

From: Lidka Maslankiewicz [mailto:lidka.maslankiewicz@rivm.nl]

**Sent:** Friday, September 22, 2017 4:54 AM **To:** Kraft, Andrew < Kraft. Andrew @epa.gov >

**Cc:** Bussard, David <<u>Bussard.David@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Els Smit <<u>els.smit@rivm.nl</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Joke Herremans <<u>joke.herremans@rivm.nl</u>>; Paul Janssen <<u>paul.janssen@rivm.nl</u>>; Thayer, Kris <thayer.kris@epa.gov>; Theo Vermeire <theo.vermeire@rivm.nl>

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Andrew and Barbara

Thank you for your reply, apologies for not answering sooner.

The issue is that we would like to use the data as presented in the 2010 Draft, more specifically the quantification of cancer risks for NPC (Nasopharyngeal Cancer), based either on human data and on animal data.

From your mail, we understand that the information is not to be cited as the EPA position. That was not our intention, but rather we want to include the unit risks as a scientific approach that has been developed and that we need to take on board.

Could it be possible to use the information, if we explicitly include a disclaimer? Something in line with: "It should be noted that the methodology used for the quantification of cancer risk for NPC (Nasopharyngeal Cancer), has not been formalised and should not be seen as the official position of the EPA. From a scientific viewpoint, however, we consider this approach as valid and use unit risk to derive the Maximum Permissible Risk (MPR)."

We also noted that in 2014 US-EPA convened a workshop (<a href="https://www.epa.gov/sites/production/files/2014-2/documents/formaldehyde-workshop-agenda-final.pdf">https://www.epa.gov/sites/production/files/2014-2/documents/formaldehyde-workshop-agenda-final.pdf</a>), the topics of which were the endogenous formation of



formaldehyde and its relation to formaldehyde toxicity and the mechanistic evidence for lymphohematopoietic cancer induction by formaldehyde. Any further information on these topics and on the envisaged timeline for finalization of the US-EPA IRIS evaluation would be very welcome.

Maybe we can first do the exchange via mail and decide later on if a telephone conference is useful.

Kind regards

Lidka

Lidka Maslankiewicz
National Institute for Public Health and the Environment (RIVM)
Centre for Safety of Substances and Products
tel. 31 (0)30 2743160
+31 6 46 86 07 73
fax. 31 (0)30 2744401
e-mail: Lidka.Maslankiewicz@rivm.nl

From: "Kraft, Andrew" < Kraft.Andrew@epa.gov>

To: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl >,

Els Smit <<u>els.smit@rivm.nl</u>>, Paul Janssen <<u>paul.janssen@rivm.nl</u>>, "Joke Herremans" <<u>joke.herremans@rivm.nl</u>>, "Glenn, Barbara"

<<u>Glenn Barbara@epa.gov>, "D'Amico, Louis" <DAmico Louis@epa.gov>, "Bussard, David" <Bussard David@epa.gov>, "Thayer, Kris" <thayer.kris@epa.gov></u>

Date: 09/08/2017 05:21 PM

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Hi Lidka,

Barbara (Glenn) and I are the current chemical managers of the formaldehyde assessment. We were hoping we might be able to set up a phone conversation to talk through the current status of the assessment and your questions below? If so, I can send out some type of Google poll or similar to find a time that works for everyone who might want to participate?

I would emphasize to you that the draft you mention was never finalized after it was released for the purposes of peer consultation and review. Thus, it should not be cited as an EPA position. We can explain this in greater detail when we talk.

We look forward to future conversations, Andrew and Barbara

From: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl>

Sent: Tuesday, August 29, 2017 7:59 AM

To: Kraft, Andrew

Cc: Els Smit; Paul Janssen; Joke Herremans

Subject: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)



Dear Dr Kraft,

My name is Lidka Maslankiewicz and I work at the Dutch National Institute for Public Health and the Environment (RIVM). We are currently busy with the update of the Maximum Permissible Risk (MPR) for formaldehyde.

We would like to use the approach and values described in IRIS Toxicological Review of Formaldehyde (Inhalation) (External Review Draft 2010), in particular Volume 3: "Quantitative Assessment, Major Conclusions in the Characterization of Hazard and Dose Response"

(<a href="https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614">https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614</a>), to derive MPR value for the Netherlands. Could you, please, inform me, if this could be permitted? Are there more recent versions of this document? If we would be allowed to use your data, how we could refer to the source?

#### IRIS Toxicological Review of Formaldehyde (Inhalation ...

cfpub.epa.gov

EPA announces the release of the Toxicological Review of Formaldehyde-Inhalation Assessment in the June 2, 2010 Federal Register Notice. This draft assessment is ...

#### Kind regards

Lidka

Lidka Maslankiewicz

National Institute for Public Health and the Environment (RIVM)

Centre for Safety of Substances and Products

tel. 31 (0)30 2743160

+31 6 46 86 07 73

fax. 31 (0)30 2744401

e-mail: Lidka.Maslankiewicz@rivm.nl

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te meiden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

www.rivm.ni De zorg voor morgen begint vandaag

| <u>rivm</u>                                                                 |
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| <u>www.rivm.nl</u>                                                          |
| Dit Nederlandse overheidsinstituut verzorgt informatie, monitoring en       |
| wetenschappelijke onderbouwing van het volksgezondheidsbeleid. Ook valt het |
| nformatiecentrum                                                            |

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|                                         | www.rivm.nl                                                                 |
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|                                         | knowledge institutes have joined forces to provide practical, demand-driven |
|                                         | policy advice based                                                         |

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|   | www.rivm.nl                                                                 |
|   | Dutch experts on climate change adaptation join forces. Fourteen Dutch      |
|   | knowledge institutes have joined forces to provide practical, demand-driven |
|   | policy advice based                                                         |

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te melden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

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This message may contain information that is not intended for you. If you are not the addressee or if this message was sent to you by mistake, you are requested to inform the sender and delete the message. RIVM accepts no liability for damage of any kind resulting from the risks inherent in the electronic transmission of messages.

www.rivm.nl/en Committed to health and sustainability



From: Bussard, David [Bussard.David@epa.gov]

**Sent**: 10/26/2017 3:21:13 PM

To: Keshava, Nagalakshmi [Keshava.Nagu@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]

CC: Glenn, Barbara [Glenn.Barbara@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; D'Amico, Louis

[DAmico.Louis@epa.gov]

**Subject**: RE: A few more details re formaldehyde conference discussion on caffeine

### Ex. 5 - Deliberative Process

יטועגטי

From: Keshava, Nagalakshmi

Sent: Thursday, October 26, 2017 7:49 AM

To: Bussard, David <Bussard.David@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; D'Amico,

Louis <DAmico.Louis@epa.gov>

Subject: RE: A few more details re formaldehyde conference discussion on caffeine

Thanks David.

Iris information helpful.

Ex. 5 - Deliberative Process

### Ex. 5 - Deliberative Process

From: Bussard, David

**Sent:** Wednesday, October 25, 2017 5:48 PM **To:** Kraft, Andrew < <u>Kraft.Andrew@epa.gov</u>>

Cc: Keshava, Nagalakshmi < Keshava. Nagu@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Ramasamy,

Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>> **Subject:** Re: A few more details re formaldehyde conference discussion on caffeine

#### Ex. 5 - Deliberative Process

David Bussard

On Oct 25, 2017, at 4:31 PM, Kraft, Andrew < Kraft. Andrew@epa.gov > wrote:



### Ex. 5 - Deliberative Process

From: Bussard, David

Sent: Wednesday, October 25, 2017 4:08 PM

**To:** Keshava, Nagalakshmi; Kraft, Andrew; Glenn, Barbara; Ramasamy, Santhini **Subject:** A few more details re formaldehyde conference discussion on caffeine

#### **David Bussard**

#### Begin forwarded message:

From: "Camacho, Iris" < Camacho.Iris@epa.gov > Date: October 25, 2017 at 2:47:46 PM EDT

To: "Bussard, David" < Bussard.David@epa.gov >

Subject: RE: by any chance, do you have notes on formaldehyde

conference discussion on caffeine?

#### David,

J. Bus mentioned that caffeine undergoes demethylation to formaldehyde. He also mentioned that 400 mg dose of caffeine (on a daily basis) releases ~2 mmoles of formaldehyde. No reference was provided about this information.

He and others were making the point how data from chemicals systemically metabolized into formaldehyde might inform the MoA for leukemia. He also mentioned methyl chloride.

Iris A. Camacho, Ph.D.

Senior Science Advisor (on detail)



Office of Pollution Prevention and Toxics

U.S. Environmental Protection Agency

William Jefferson Clinton Building East, 6308-A

Washington, DC 20460

Phone: 202-564-1229

Work hours: 8:00 am - 4:30 pm

Work cell phone: Ex. 6 - Personal Privacy

Telework phone: Ex. 6 - Personal Privacy

Email: camacho.iris@epa.gov

From: Bussard, David

**Sent:** Tuesday, October 24, 2017 12:17 PM **To:** Camacho, Iris < Camacho.Iris@epa.gov>

Subject: Re: by any chance, do you have notes on formaldehyde

conference discussion on caffeine?

Thx. I know times are busy!

**David Bussard** 

On Oct 24, 2017, at 11:54 AM, Camacho, Iris < <a href="mailto:Camacho.Iris@epa.gov">Camacho.Iris@epa.gov</a>> wrote:

David,

I will check my notes and get back to you tomorrow. It may be earlier but no promises.

-Iris Camacho



From: Bussard, David

**Sent:** Tuesday, October 24, 2017 11:23 AM **To:** Camacho, Iris < Camacho.Iris@epa.gov > **Subject:** by any chance, do you have notes on formaldehyde conference discussion on caffeine?

Iris,

Kris said she'd stepped out during the discussion of caffeine. By any chance do you have notes that would share insight as to what the argument is? It is not one I recall anyone making to NCEA in the past with respect to caffeine. But, we are just trying to anticipate issues that could arise. We'll look for what we can find in the open literature re metabolism of caffeine (the first step is a demethylation and there is work showing labeled caffeine results in labeled CO2 in exhaled breath), but are not sure what the argument made was.

I know you are busy. But, if you have a chance and have any insights, that would be useful.

**David Bussard** 



From: Glenn, Barbara [Glenn.Barbara@epa.gov]

**Sent**: 10/23/2017 6:49:16 PM **To**: riesd@michigan.gov

CC: Kraft, Andrew [Kraft.Andrew@epa.gov]

Subject: RE: Question about formaldehyde assessment

Hi Divinia,

We are certainly hoping that the document will be made available for public comment in the later part of 2018. Thank you for your patience.

Regards, Barbara

From: Ries, Divinia (DEQ) [mailto:RIESD@michigan.gov]

**Sent:** Monday, October 23, 2017 2:20 PM **To:** Glenn, Barbara <Glenn.Barbara@epa.gov>

Subject: RE: Question about formaldehyde assessment

Hi Barbara,

Thank you for your response. Do you have an idea when the draft will be posted for public comment? We are leaning towards applying the mutagenic mode of action for formaldehyde based on the NRC report:

Page 161: The committee concludes that the systemic genotoxic and mutagenic mode of action of formaldehyde is sufficiently supported by the evidence from studies of humans exposed to formaldehyde. The committee acknowledges that reporting bias against negative results could be a limitation of its approach to reviewing the mechanistic evidence (NRC 2014); however, that limitation does not detract from the conclusion that formaldehyde can induce systemic genotoxic changes.

It would help us to know what IRIS's direction on this matter once you publish the draft. More power to you and your team.

Again, thank you for the good work you do.

Divinia

Divinia Nolasco Ries, MPH, MS, Ph.D.

Toxicology Specialist
Remediation and Redevelopment Division
Department of Environmental Quality
P.O. Box 30426
Lansing MI 48909-7926

Phone#: 517-284-5142 riesd@michigan.gov

From: Glenn, Barbara [mailto:Glenn.Barbara@epa.gov]

**Sent:** Monday, October 23, 2017 9:41 AM

**To:** Ries, Divinia (DEQ)

Cc: Kraft, Andrew; Bussard, David; Ramasamy, Santhini; Soto, Vicki; Rieth, Susan; Radke-Farabaugh, Elizabeth; D'Amico,



Louis; Subramaniam, Ravi

**Subject:** Question about formaldehyde assessment

Dear Dr. Ries,

As team leaders for the formaldehyde assessment, we are responding to your letter dated 10/06/17 to the IRIS Hotline. We apologize for the delayed response to your inquiry about the formaldehyde assessment. Our revision of the formaldehyde assessment is almost complete and will be ready to begin our review process soon. The review process is comprehensive; it involves review by other offices within EPA, review by other federal agencies, a public comment period, as well as an independent peer review that, for this assessment, will be conducted by the National Academies of Sciences. Given the timelines necessary to complete these steps, we do not expect that the final assessment will be posted during 2018.

You also asked about whether we will be changing conclusions about the mutagenic mode-of-action for the IUR. At this point, we regret that we are not able to discuss the specifics of the conclusions in the document.

Sincerely, Barbara Glenn and Andrew Kraft



From: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]

**Sent**: 11/30/2017 2:38:46 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]

**Subject**: RE: Hot off the press on Endogenous Formaldehyde

Noted...

Re. the Appendices, I have lots of edits (much of them deletions) to make. But I would not get to that until Dec 11.

Ravi Subramaniam
RRB 51237/ (202) 564-2445 (o), (Ex. 6 - Personal Privacy

From: Kraft, Andrew

Sent: Thursday, November 30, 2017 9:33 AM

To: Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Bussard, David <Bussard.David@epa.gov>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Vulimiri,

Suryanarayana < Vulimiri. Sury@epa.gov>

Subject: RE: Hot off the press on Endogenous Formaldehyde

Hi Ravi, good question. It is just too problematic at this point for you to be working in the master versions (on Sharepoint) that Barbara and I are working on.

So, I have attached here a current copy of the main draft and overview documents. Please crosswalk any changes across both documents, and let us know if you also need to make changes to the Appendices (which you can probably work on directly in Sharepoint, as we are not yet working on them).

Since it sounds like you will be working on making changes before Sury, we would prefer if you could make your edits in track changes and then send the docs to Sury, who can then send the docs back to us (or something similar).

Thanks!

From: Subramaniam, Ravi

Sent: Thursday, November 30, 2017 9:09 AM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; Bussard, David < Bussard. David@epa.gov>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Vulimiri,

Suryanarayana < Vulimiri. Sury@epa.gov>

Subject: RE: Hot off the press on Endogenous Formaldehyde

I have set aside some time this morning for formaldehyde, and will add this to my agenda. However, I would only add a few sentences to the bottom up part. Someone else, Sury perhaps?, needs to add, if necessary, elsewhere.

Andrew, how should I do this (and the other edits I have promised)? Directly, or send you the blurb separately?





From: Kraft, Andrew

Sent: Thursday, November 30, 2017 7:56 AM

To: Subramaniam, Ravi < Subramaniam.Ravi@epa.gov >; Bussard, David < Bussard.David@epa.gov >

Cc: Glenn, Barbara < Glenn.Barbara@epa.gov>; Ramasamy, Santhini < Ramasamy.Santhini@epa.gov>; Vulimiri,

Suryanarayana < Vulimiri.Sury@epa.gov>

Subject: RE: Hot off the press on Endogenous Formaldehyde

So, what do we need to add to the tox review/ appendices/ overview to close the loop?

Thanks for sharing, Sury!

From: Subramaniam, Ravi

**Sent:** Thursday, November 30, 2017 7:26 AM **To:** Bussard, David <<u>Bussard.David@epa.gov</u>>

Cc: Kraft, Andrew < Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Ramasamy, Santhini

< Ramasamy. Santhini@epa.gov >

Subject: Re: Hot off the press on Endogenous Formaldehyde

# Ex. 5 - Deliberative Process

--Kavi

Ravi Subramaniam, Ph.D.

Chief, Toxic Effects Branch, IRIS, NCEA, EPA

RRB 51237/ (202) 564-2445 (O) / Ex. 6 - Personal Privacy (m)

On Nov 30, 2017, at 7:04 AM, Bussard, David < Bussard. David@epa.gov > wrote:

Ravi

## Ex. 5 - Deliberative Process

David Bussard

Begin forwarded message:

From: "Vulimiri, Suryanarayana" < <u>Vulimiri.Sury@epa.gov</u>>

**Date:** November 29, 2017 at 5:39:41 PM EST **To:** "Bussard, David" <Bussard.David@epa.gov>

Subject: RE: Hot off the press on Endogenous Formaldehyde



Sury

**Sury Vulimiri, Ph.D., DABT** National Center for Environmental Assessment, Office of Research & Development, US EPA. Phone: 919-541-3558 | Fax: 919-541-0245 | <u>vulimiri.sury@epa.gov</u>

From: Bussard, David

**Sent:** Wednesday, November 29, 2017 5:06 PM **To:** Vulimiri, Suryanarayana < <u>Vulimiri.Sury@epa.gov</u>>

Subject: RE: Hot off the press on Endogenous Formaldehyde

Thanks Sury

## Ex. 5 - Deliberative Process

David

From: Vulimiri, Suryanarayana

Sent: Wednesday, November 29, 2017 4:43 PM

To: Bateson, Thomas < Bateson. Thomas@epa.gov >; Glenn, Barbara

<<u>Glenn.Barbara@epa.gov</u>>; Fritz, Jason <<u>Fritz.Jason@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Makris, Susan <<u>Makris, Susan@epa.gov</u>>; Segal, Deborah



<Segal.Deborah@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>;

Vulimiri, Suryanarayana < Vulimiri. Sury@epa.gov>; Whalan, John

<Whalan.John@epa.gov>

Cc: Bussard, David < Bussard. David@epa.gov >; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>

Subject: Hot off the press on Endogenous Formaldehyde

Nature, 2017 Aug 31;548(7669):549-554, doi: 10.1038/nature23481, Epub 2017 Aug 16.

## Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism.

Burgos-Barragan G<sup>1</sup>, Wit N<sup>1</sup>, Meiser J<sup>2</sup>, Dingler FA<sup>1</sup>, Pietzke M<sup>2</sup>, Mulderrig L<sup>1</sup>, Pontel LB<sup>1</sup>, Rosado IV<sup>2</sup>, Brewer TF<sup>2</sup>, Cordell RL<sup>2</sup>, Monks PS<sup>2</sup>, Chang CJ<sup>2</sup>, Vazquez A<sup>2</sup>, Patel KJ<sup>2</sup>.

#### **Author information**

1

MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge CB2 0QH, UK.

2

Cancer Research UK Beatson Institute, Glasgow G61 1BD, UK.

3

Instituto de Biomedicina de Sevilla (IBiS) Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, 41013 Seville, Spain.

4

Department of Chemistry, Department of Molecular and Cell Biology, and Howard Hughes Medical Institute, University of California, Berkeley, Berkeley, California 94720, USA.

5

Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK.

6

University of Cambridge, Department of Medicine, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.

#### **Abstract**

The folate-driven one-carbon (1C) cycle is a fundamental metabolic hub in cells that enables the synthesis of nucleotides and amino acids and epigenetic modifications. This cycle might also release formaldehyde, a potent protein and DNA crosslinking agent that organisms produce in substantial quantities. Here we show that supplementation with tetrahydrofolate, the essential cofactor of this cycle, and other oxidation-prone folate derivatives kills human, mouse and chicken cells that cannot detoxify formaldehyde or that lack DNA crosslink repair. Notably, formaldehyde is generated from oxidative decomposition of the folate backbone. Furthermore, we find that formaldehyde detoxification in human cells generates formate, and thereby promotes nucleotide synthesis. This supply of 1C units is sufficient to sustain the growth of cells that are unable to use serine, which is the predominant source of 1C units. These findings identify an unexpected source of formaldehyde and, more generally, indicate that the detoxification of this ubiquitous endogenous genotoxin creates a benign 1C unit that can sustain essential metabolism.

PMID: 28813411

DOI:

10.1038/nature23481

<< File: Burgos-Barragan et al 2017\_EndogenouFA.pdf >> << File: Pontel et al 2015\_SV.pdf >>



So the bottom line is that endogenous formaldehyde is safely handled by the cells diverting it into normal cellular metabolism. This is published in Nature (PDF attached).

Does this mean there is no need to worry about endogenous formaldehyde for making any adjustments for risk assessment when dealing with exogenous formaldehyde?

One of the co-authors is Pontel, who published earlier an article titled "Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen" in the Journal 'Molecular Cell' on which Dr. Swenberg is a co-author.

Sury

**Sury Vulimiri, Ph.D., DABT** National Center for Environmental Assessment, Office of Research & Development, US EPA. Phone: 919-541-3558 | Fax: 919-541-0245 | <u>vulimiri.sury@epa.gov</u>



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 9/8/2017 1:42:42 PM

To: Bussard, David [Bussard.David@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]; Ramasamy, Santhini

[Ramasamy.Santhini@epa.gov]

Subject: Re: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of Formaldehyde

(Inhalation)

# Ex. 5 - Deliberative Process

From: Bussard, David

Sent: Thursday, September 7, 2017 9:22 PM

To: Kraft, Andrew; Glenn, Barbara; Ramasamy, Santhini

Subject: FW: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

See below.

# Ex. 5 - Deliberative Process

David

From: Bahadori, Tina

**Sent:** Thursday, August 31, 2017 12:07 PM

To: Ross, Mary <Ross.Mary@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma

<Lavoie.Emma@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>;

Hagerthey, Scot < Hagerthey. Scot@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

### Ex. 5 - Deliberative Process

From: Ross, Mary

**Sent:** Thursday, August 31, 2017 12:05 PM

To: Bussard, David < Bussard. David@epa.gov >; Bahadori, Tina < Bahadori. Tina@epa.gov >; Lavoie, Emma

<<u>Lavoie.Emma@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>;

Hagerthey, Scot < Hagerthey.Scot@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)



EPA-18-0076-A-000401

From: Bussard, David

**Sent:** Thursday, August 31, 2017 12:00 PM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Lavoie, Emma

<<u>Lavoie.Emma@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>;

Hagerthey, Scot < Hagerthey.Scot@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

## Ex. 5 - Deliberative Process

David

From: Bahadori, Tina

Sent: Thursday, August 31, 2017 11:49 AM

To: Ross, Mary < Ross. Mary@epa.gov>; Lavoie, Emma < Lavoie. Emma@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>;

Hagerthey, Scot < Hagerthey.Scot@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

:::we'll need a conversation. The space is systematic review.

From: Ross, Mary

Sent: Thursday, August 31, 2017 11:48 AM

To: Bahadori, Tina < Bahadori. Tina@epa.gov >; Lavoie, Emma < Lavoie. Emma@epa.gov >; Bussard, David

<<u>Bussard.David@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>;

Hagerthey, Scot < Hagerthey.Scot@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

#### Ex. 5 - Deliberative Process

From: Bahadori, Tina

Sent: Thursday, August 31, 2017 11:46 AM

To: Ross, Mary <Ross.Mary@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bussard, David

< Bussard. David@epa.gov >; Jones, Samantha < Jones. Samantha@epa.gov >; D'Amico, Louis < DAmico. Louis@epa.gov >;

Hagerthey, Scot < Hagerthey. Scot@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)



From: Ross, Mary

Sent: Thursday, August 31, 2017 11:35 AM

To: Lavoie, Emma < Lavoie. Emma@epa.gov >; Bussard, David < Bussard. David@epa.gov >; Bahadori, Tina

<Bahadori.Tina@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>;

Hagerthey, Scot <hagerthey.Scot@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

## Ex. 5 - Deliberative Process

From: Lavoie, Emma

Sent: Thursday, August 31, 2017 10:56 AM

To: Bussard, David <<u>Bussard.David@epa.gov</u>>; Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>; Ross, Mary

< Ross. Mary@epa.gov>; Jones, Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>;

Hagerthey, Scot < Hagerthey.Scot@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

Being that schedules are tight today a couple of thoughts from me on email:

| 1 | ) David's | proposed re | sponse is reasonal | ы | e |
|---|-----------|-------------|--------------------|---|---|
|   |           |             |                    |   |   |

| 2) | Ex. 5 - Deliberative Process |
|----|------------------------------|
|    | \                            |

-Emma

Emma T. Lavoie, PhD Tel: 703-347-0328

From: Bussard, David

Sent: Thursday, August 31, 2017 8:30 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>;

Hagerthey, Scot < Hagerthey.Scot@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: Fwd: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of

Formaldehyde (Inhalation)

I have not gotten much by way of email brainstorming. This should be an IO decision, so I'll now pass it up to the IO.

## Ex. 5 - Deliberative Process



EPA-18-0076-A-000403

One attempt to craft a response is in email below.

#### David Bussard

Begin forwarded message:

From: "Jones, Samantha" < Jones. Samantha@epa.gov>

**Date:** August 30, 2017 at 11:48:38 PM EDT

To: "Bussard, David" < Bussard. David@epa.gov>, "Birchfield, Norman"

<<u>Birchfield.Norman@epa.gov</u>>, "Ramasamy, Santhini" <<u>Ramasamy.Santhini@epa.gov</u>>,

"D'Amico, Louis" < <u>DAmico.Louis@epa.gov</u>>, "Glenn, Barbara" < <u>Glenn.Barbara@epa.gov</u>>,

"Hagerthey, Scot" < Hagerthey.Scot@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS

**Toxicological Review of Formaldehyde (Inhalation)** 

## Ex. 5 - Deliberative Process

It would be good to broach the subject with Tina before responding.

Samantha

From: Bussard, David

Sent: Wednesday, August 30, 2017 10:28 AM

**To:** Jones, Samantha < <u>Jones.Samantha@epa.gov</u>>; Birchfield, Norman < <u>Birchfield.Norman@epa.gov</u>>; Ramasamy, Santhini < <u>Ramasamy.Santhini@epa.gov</u>>; D'Amico, Louis < <u>DAmico.Louis@epa.gov</u>>; Glenn,

Barbara < Glenn.Barbara@epa.gov>; Hagerthey, Scot < Hagerthey.Scot@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological

Review of Formaldehyde (Inhalation)

Asking their timeframe could be part of a response, or a first step. (I don't know it, and the email Andrew got does not say their timeframe.)

From: Jones, Samantha

Sent: Wednesday, August 30, 2017 10:14 AM

**To:** Bussard, David < <u>Bussard.David@epa.gov</u>>; Birchfield, Norman < <u>Birchfield.Norman@epa.gov</u>>; Ramasamy, Santhini < <u>Ramasamy.Santhini@epa.gov</u>>; D'Amico, Louis < <u>DAmico.Louis@epa.gov</u>>; Glenn,

Barbara < Glenn.Barbara@epa.gov >; Hagerthey, Scot < Hagerthey.Scot@epa.gov >

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological

Review of Formaldehyde (Inhalation)

There is an opportunity here. Do we have any idea about their timeframe??

Samantha Jones, PhD
NCEA Associate Director for Health (acting)
HHRA Interim Deputy National Program Director
USEPA, ORD/NCEA
703-347-8580

From: Bussard, David

Sent: Wednesday, August 30, 2017 10:10 AM



**To:** Birchfield, Norman <a href="mailto:size:line"><u>Birchfield.Norman@epa.gov</u></a>; Ramasamy, Santhini <a href="mailto:size:line"><u>Ramasamy.Santhini@epa.gov</u></a>; D'Amico, Louis <a href="mailto:DAmico.Louis@epa.gov">DAmico.Louis@epa.gov</a>; Glenn, Barbara <a href="mailto:size:line"><u>Glenn.Barbara@epa.gov</u></a>; Hagerthey, Scot <a href="mailto:size:line"><u>Hagerthey.Scot@epa.gov</u></a>; Jones, Samantha <a href="mailto:size:line">Jones.Samantha@epa.gov</a>>

**Subject:** FW: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of Formaldehyde (Inhalation)

This is likely "a Tina issue", but let's see if we can generate a recommendation or some options.

Is this a possible response?

## Ex. 5 - Deliberative Process

David

From: Kraft, Andrew

Sent: Wednesday, August 30, 2017 8:04 AM

To: Birchfield, Norman <Birchfield.Norman@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>

Cc: Bussard, David <Bussard.David@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Glenn, Barbara

<Glenn.Barbara@epa.gov>

Subject: Fw: Request for permission to use data from IRIS Toxicological Review of Formaldehyde

(Inhalation)

I'm guessing we will need a fairly quick and succinct response. Please forward as appropriate.

-Andrew

From: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl>

Sent: Tuesday, August 29, 2017 7:59 AM

To: Kraft, Andrew

**Cc:** Els Smit; Paul Janssen; Joke Herremans

Subject: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)



#### Dear Dr Kraft,

My name is Lidka Maslankiewicz and I work at the Dutch National Institute for Public Health and the Environment (RIVM). We are currently busy with the update of the Maximum Permissible Risk (MPR) for formaldehyde. We would like to use the approach and values described in IRIS Toxicological Review of Formaldehyde (Inhalation) (External Review Draft 2010), in particular Volume 3: "Quantitative Assessment, Major Conclusions in the Characterization of Hazard and Dose Response" (<a href="https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614">https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614</a>), to derive MPR value for the Netherlands. Could you, please, inform me, if this could be permitted? Are there more recent versions of this document? If we would be allowed to use your data, how we could refer to the source?

### IRIS Toxicological Review of Formaldehyde (Inhalation ...

### cfpub.epa.gov

EPA announces the release of the Toxicological Review of Formaldehyde-Inhalation Assessment in the June 2, 2010 Federal Register Notice. This draft assessment is ...

Kind regards
Lidka
Lidka Maslankiewicz
National Institute for Public Health and the Environment (RIVM)
Centre for Safety of Substances and Products
tel. 31 (0)30 2743160
+31 6 46 86 07 73
fax. 31 (0)30 2744401

e-mail: Lidka.Maslankiewicz@rivm.nl

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te meiden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

www.rivm.nl De zorg voor morgen begint vandaag

| RIVM                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| www.rivm.nl                                                                                                                                                                                 |
| Dit Nederlandse<br>overheidsinstituut<br>verzorgt informatie,<br>monitoring en<br>wetenschappelijke<br>onderbouwing van het<br>volksgezondheidsbeleid.<br>Ook valt het<br>informatiecentrum |



message. RIVM accepts no liability for damage of any kind resulting from the risks inherent in the electronic transmission of messages. www.rivm.nl/en Committed to health and sustainability Rijksinstituut voor Volksgezondheid en Milieu - RIVM www.rivm.nl Substances of very high concern hamper recycling. Substances of very high concern (SVHC) can hamper the safe recycling of waste streams in the Netherlands. Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te meiden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het eiektronisch verzenden van berichten. www.rivm.ni De zorg voor morgen begint vandaag RIVM www.rivm.nl Dit Nederlandse overheids in stituut verzorgt informatie, monitoring en

This message may contain information that is not intended for you. If you are not the addressee or if this message was sent to you by mistake, you are requested to inform the sender and delete the message. RIVM accepts no liability for damage of any kind resulting from the risks inherent in the electronic transmission of messages.

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wetenschappelijke onderbouwing van het volksgezondheidsbeleid.

informatiecentrum ...

Ook valt het

| Rijksinstituut                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------|
| voor                                                                                                               |
| Volksgezondheid                                                                                                    |
| en Milieu - RIVM                                                                                                   |
| www.rivm.nl                                                                                                        |
| Substances of very high<br>concern hamper<br>recycling. Substances o<br>very high concern<br>(SVHC) can hamper the |
| <br>safe recycling of waste<br>streams in the<br>Netherlands.                                                      |



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 10/16/2017 10:53:44 AM

To: Morgan, Daniel (NIH/NIEHS) [E] [morgand@niehs.nih.gov]

**CC**: Glenn, Barbara [Glenn.Barbara@epa.gov]

**Subject**: Re: Clarification of NTP report (released in August, 2017)

Thank you, Dan, that is very helpful contextual information.

Thanks again for sharing and best of luck with your ongoing research.

Best,

-Andrew

From: Morgan, Daniel (NIH/NIEHS) [E] <morgand@niehs.nih.gov>

Sent: Friday, October 13, 2017 10:15 AM

To: Kraft, Andrew

Cc: Glenn, Barbara; Morgan, Daniel (NIH/NIEHS) [E]

**Subject:** RE: Clarification of NTP report (released in August, 2017)

#### Hi Andrew,

Hope you are doing well. Selection of an 8-week exposure duration was based upon both scientific and practical considerations. The formaldehyde study was initially planned to be a collaborative effort between NIEHS and the EPA in Research Triangle Park; however, the exposure chambers at the EPA inhalation facility were only available to us for 8 weeks. Based upon the HSPC doubling time, the high exposure concentrations used, and the availability of exposure chambers, the 8-week exposure duration was selected. A study protocol was approved and signed. However, after a number of bureaucratic delays, the decision was made to conduct the studies at the NIEHS inhalation facility using the same approved protocol.

In a dose-range-finding study, significant necrosis, squamous metaplasia, and regeneration of respiratory epithelium was present in the nasal cavity after exposure for 2-weeks to 5, 10, and 20 ppm FA. Body weights were decreased by 7% and 12% in mice exposed to 10 and 20 ppm, respectively. Based upon the 2-week study data, exposure to a high concentration of 15 ppm for 8 weeks was expected to be close to the MTD.

Exposure for 8 weeks to 7.5 and 15 ppm FA significantly decreased body weight gain of mice indicating that an MTD was attained in this time period. Although a longer exposure may have been more acceptable, the amount of squamous metaplasia and keratin deposition in the nose after only 8-weeks suggests that the potential for FA to penetrate the nasal tissue and contact with HSPC cells would continue to decrease with longer exposure durations.

I hope this information is helpful. Please call me if you need further clarification or more information. Thanks.

Dan

(919) 541-2264

From: Kraft, Andrew [mailto:Kraft.Andrew@epa.gov]

Sent: Thursday, October 12, 2017 1:38 PM

To: Morgan, Daniel (NIH/NIEHS) [E] <morgand@niehs.nih.gov>



**Cc:** waalkes@mail.nih.gov; Glenn, Barbara <Glenn.Barbara@epa.gov> **Subject:** Clarification of NTP report (released in August, 2017)

Dear Drs. Morgan and Waalkes,

As you are probably aware, the IRIS Program at EPA is conducting a human health assessment of inhaled formaldehyde. Barbara Glenn and myself are the co-chemical managers. A key focus of the assessment is on the carcinogenic potential of formaldehyde exposure. The research report from your division that was released in August titled, "Absence of formaldehyde-induced neoplasia in TRP53 haploinsufficient mice exposure by inhalation" has been brought to our attention and I was hoping that you might be able to provide some clarifying information now that it is publicly available (I spoke with you at your poster on this study at SOT several years back).

The primary reason I wanted to contact you relates to the selected exposure duration of 8 weeks. Acknowledging that rat models were not available, and as you noted in your report, mice appear to be less sensitive to the potential carcinogenicity of formaldehyde, both in terms of exposure level and duration (e.g., including the amount of time after exposure starts before tumors begin to appear, but noting that although it would be ideal if the examinations were longer than 1 year, I understand that this was constrained by background tumors in these mice). In addition, I noticed that all of the previous carcinogenicity studies using these mice that were cited in the report employed exposure durations longer than 26 weeks (most were 35-40 weeks). Can you provide any additional explanation for the 8 week exposure duration than what is already in the report (e.g., about the HSPC doubling time)? I did notice in the report that, at least at 15ppm, you indicated that the maximally tolerated cumulative dose appeared to be 8 weeks; were the exposures intentionally ceased at that point of the study?

Thank you for any explanation, clarification, or insight you can provide. If it would be easier to discuss over the phone, Barbara and I would be happy to give you a call.

Otherwise, I hope that you are settling into Fall, and that your research (or retirement) is going well. I look forward to hearing from you.

Best regards, Andrew

National Center for Environmental Assessment U.S. Environmental Protection Agency Washington, DC (703)347-0221



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 9/8/2017 1:37:41 PM

**To**: Glenn, Barbara [Glenn.Barbara@epa.gov]

Subject: Re: Program and Regional Patron or Client engagement on IRIS assessments

Awesome, this is a good start. I'd have to look back, but I think someone from CA and someone from VT also requested information (I cannot recall if they were associated with regional offices; I think just with state agencies). Norm also mentioned that there is interest from the hazardous waste side... and water was interested in it for some reason (weird)- although they've not reached out in the last year.

From: Glenn, Barbara

Sent: Friday, September 8, 2017 8:17 AM

To: Kraft, Andrew

Subject: RE: Program and Regional Patron or Client engagement on IRIS assessments

To start off,

Patrons/clients:

Office of Air: had a meeting to find out their priorities and needs re: formaldehyde 2 years ago (can't remember who was there)

Do you think she wants names or office names?

OPP: conducting a microbials rule

Meetings and communications several times this year (5?) - Timothy Leighton and Timothy Dole of OPP

Regions: Region 5 asked about the status of the formaldehyde assessment for discussion with State partners at a Regional/State meeting

Rae Trine, Air toxic and assessment branch in Region 5 – I called and spoke with her.

From: Kraft, Andrew

**Sent:** Thursday, September 07, 2017 2:54 PM **To:** Glenn, Barbara <Glenn.Barbara@epa.gov>

Subject: FW: Program and Regional Patron or Client engagement on IRIS assessments

I suppose we need to do this too...

From: Lavoie, Emma

Sent: Monday, August 28, 2017 10:03 AM

To: Davis, Allen <Davis.Allen@epa.gov>; Lee, Janice <Lee.JaniceS@epa.gov>; Gibbons, Catherine

<Gibbons.Catherine@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Arzuaga, Xabier <Arzuaga.Xabier@epa.gov>;

Weaver, Andre <Weaver, James@epa.gov>; Yost, Erin <Yost, Erin@epa.gov>; Keshava, Nagalakshmi

<Keshava.Nagu@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Segal,

Deborah < Segal. Deborah@epa.gov>; Keshava, Channa < Keshava. Channa@epa.gov>; Druwe, Ingrid

<Druwe.ingrid@epa.gov>; Li, Jenny <Li.Jenny@epa.gov>; Pardo, Larissa <Pardo.Larissa@epa.gov>; Hogan, Karen

<<u>Hogan.Karen@epa.gov</u>>; Pratt, Margaret <<u>pratt.margaret@epa.gov</u>>; Carlson, Laura <<u>Carlson.Laura@epa.gov</u>>;

Lehmann, Geniece < Lehmann. Geniece@epa.gov>



**Cc:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov">thayer.kris@epa.gov</a>; Avery, James <a href="mailto:Avery.James@epa.gov">Avery.James@epa.gov</a>; Fritz, Jason@epa.gov</a>; Soto, Vicki <a href="mailto:Soto.Vicki@epa.gov">Soto.Vicki@epa.gov</a>

Subject: Program and Regional Patron or Client engagement on IRIS assessments

IRIS assessment managers:

I'd like to check-in with you about who and how often you are engaging your clients/partners/patrons in the program and regional offices.

Please reply to me with the following information (briefly):

Who do you consider your 'patron' or 'client' in the Programs and/or Regions?

How often do you interact with them e.g., give updates, answer questions or give presentations? How often in the last 12 months?

I'll use this information to work with you to improve or refine our interactions as assessments move forward.

I have worked with some of you in the last year on Patron/client interactions but may not have discussed this much in the last few months. If an assessment manager is missing from this email, it is because I have recent activity with them regarding their Patrons or their assessment is in SAB review.

For phthalates, Erin Yost has started this conversation with me, but if you have anything specific on any part of the phthalates work, please still share it.

Otherwise I'm specifically interested in these assessments:

| Arsenic inorg   |  |  |
|-----------------|--|--|
| BBP             |  |  |
| Chromium VI     |  |  |
| DBP             |  |  |
| DEP             |  |  |
| DIBP            |  |  |
| DINP            |  |  |
| Formaldehyde    |  |  |
| Naphthalene     |  |  |
| Nitrate Nitrite |  |  |
| PAH RPFs        |  |  |

**PCBs** 

tert-Butanol

| -Emma |  |  |  |
|-------|--|--|--|
|       |  |  |  |

Emma T. Lavoie, PhD Assistant Center Director for Scientific Support National Center for Environmental Assessment US Environmental Protection Agency

Tel: 703-347-0328



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 10/11/2017 12:30:29 PM

**To**: Bateson, Thomas [bateson.thomas@epa.gov]

CC: Glenn, Barbara [glenn.barbara@epa.gov]; Bussard, David [bussard.david@epa.gov]; Ramasamy, Santhini

[Ramasamy.Santhini@epa.gov]

**Subject**: FW: Next Steps on Formaldehyde - updated schedule

### Ex. 5 - Deliberative Process

Just FYI, not for email chain discussion, as I'm sure it will come up during pre-brief.

From: Thayer, Kris

Sent: Wednesday, October 11, 2017 8:29 AM
To: Kraft, Andrew < Kraft. Andrew@epa.gov>
Cc: Glenn, Barbara < Glenn. Barbara@epa.gov>

**Subject:** Re: Next Steps on Formaldehyde - updated schedule

## Ex. 5 - Deliberative Process

Sent from my iPhone

On Oct 11, 2017, at 8:16 AM, Kraft, Andrew < <a href="mailto:Kraft\_Andrew@epa.gov">Kraft\_Andrew@epa.gov</a>> wrote:

They neither agreed nor disagreed with the conclusion. They disagreed with the grouping of "all LHP cancers" and recommended we focus on more specific diagnoses, such as AML. Their main concern was that there appeared to be no clear framework for drawing causal conclusions, and so they were unable to clearly gauge and evaluate EPA's support for the conclusion in the prior draft.

From: Thayer, Kris

Sent: Wednesday, October 11, 2017 8:08 AM To: Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft, Andrew@epa.gov</a> Cc: Glenn, Barbara@epa.gov>

Subject: Re: Next Steps on Formaldehyde - updated schedule

Sorry to be remedial but remind me what the conclusion was in 2011 and NAS opinion of the conclusion?

Sent from my iPhone

On Oct 11, 2017, at 7:49 AM, Kraft, Andrew < Kraft. Andrew@epa.gov> wrote:

### Ex. 5 - Deliberative Process

From: Thayer, Kris

Sent: Wednesday, October 11, 2017 7:12 AM



**To:** Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov</a>>; Glenn, Barbara < <a href="mailto:Glenn.Barbara@epa.gov">Glenn.Barbara@epa.gov</a>>> **Subject:** RE: Next Steps on Formaldehyde - updated schedule

## Ex. 5 - Deliberative Process

<image001.png>

From: Bahadori, Tina

Sent: Friday, October 6, 2017 2:40 PM

To: Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn,

Barbara < Glenn. Barbara@epa.gov>

**Cc:** Ramasamy, Santhini < Ramasamy.Santhini@epa.gov>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico,

Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>; Bussard, David

<Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule



Thanks again for being so very great – all of you.

Tina

From: Soto, Vicki

Sent: Thursday, October 5, 2017 8:20 AM

To: Kraft, Andrew < Kraft Andrew@epa.gov >; Glenn, Barbara < Glenn.Barbara@epa.gov >;

Bahadori, Tina <Bahadori, Tina@epa.gov>

**Cc:** Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico, Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

Just throwing in my 2 more cents. I realize that the schedule is fluid and the further out you go, the more wishy-washy it gets, the program still needs some sort of place holder for some of these milestones.

From: Kraft, Andrew

Sent: Thursday, October 05, 2017 8:13 AM

To: Soto, Vicki <Soto. Vicki@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>;

Bahadori, Tina < Bahadori, Tina@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico,

Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>; Bussard, David

<Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>

**Subject:** RE: Next Steps on Formaldehyde - updated schedule

### Ex. 5 - Deliberative Process

Patiently,
Andrew and (speaking for) Barbara



From: Soto, Vicki

Sent: Wednesday, October 04, 2017 8:03 PM

To: Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>
Cc: Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>; Thayer, Kris

<thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

Hi everyone,

I tried to take the bullets below and wrap them into the schedule of Formaldehyde in Project. I've thrown in some highlighting to pull attention to some of those dates. I think it seems really tight. The lines that are 0 duration are milestones (for reports-most of them are a brown color) and can be ignored. This can always be altered if it doesn't make sense.

Vicki





From: Glenn, Barbara

Sent: Thursday, September 28, 2017 11:24 AM

**To:** Bahadori, Tina <a href="mailto:Sahadori.Tina@epa.gov">Sahadori.Tina@epa.gov">Sahadori.Tina@epa.gov</a>; Kraft, Andrew <a href="mailto:Kraft.Andrew@epa.gov">Kraft, Andrew@epa.gov</a>; Bussard, David <a href="mailto:Sussard.David@epa.gov">Sussard.David@epa.gov</a>; Thayer, Kris <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>; Lavoie, Emma <a href="mailto:Lavoie.Emma@epa.gov">Lavoie.Emma@epa.gov</a>

**Cc:** Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

Hi Tina,

## Ex. 5 - Deliberative Process

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 11:10 AM

**To:** Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov</a>; Glenn, Barbara < <a href="mailto:Glenn.Barbara@epa.gov">Glenn, Barbara <a href="mailto:Glenn.Barbara@epa.gov">Klenn, Barbara <a href="mailto:Glenn.Barbara@epa.gov">Glenn, Barbara <a href="mailto:Glenn.Barbara@epa.gov">Glenn.Barbara <a href="mailto:Glenn.Barbara@epa.gov">Glenn.Barbara <

Emma <<u>Lavoie.Emma@epa.gov</u>>

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary
<Ross.Mary@epa.gov>

Thanks Andrew. So, with this timeline, can we nunctuate the rest of the timeline?...

Subject: RE: Next Steps on Formaldehyde



Tina

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 10:35 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Glenn, Barbara

<Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >; Soto, Vicki

<Soto.Vicki@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Jones, Samantha

<Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Ross, Mary

<Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hi Tina,

## Ex. 5 - Deliberative Process

-Barbara and Andrew

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:05 PM

**To:** Glenn, Barbara < Glenn.Barbara@epa.gov>; Kraft, Andrew < Kraft.Andrew@epa.gov>; Bussard, David < Bussard.David@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>; Lavoie,

Emma <Lavoie.Emma@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha



<Jones.Samantha@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Thanks Barbara. This is a good timeline.

Ex. 5 - Deliberative Process

### Ex. 5 - Deliberative Process

Τ.

From: Glenn, Barbara

Sent: Tuesday, September 26, 2017 9:03 AM

**To:** Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft, Andrew@epa.gov</u>>; Bussard, David <<u>Bussard, David@epa.gov</u>>; Thayer, Kris <<u>thayer, kris@epa.gov</u>>; Lavoie,

Emma < Lavoie. Emma@epa.gov>

**Cc:** Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <DAmico.Louis@epa.gov>; Ross, Mary

<Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hello Tina,

### Ex. 5 - Deliberative Process

Thanks, Andrew and Barbara

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 8:27 AM

**To:** Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft, Andrew@epa.gov</a>; Glenn, Barbara < <a href="mailto:Glenn.Barbara@epa.gov">Glenn, Barbara < a href

Emma < Lavoie. Emma@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>

**Subject:** FW: Next Steps on Formaldehyde

Hi Everyone,



Just so we are all on the same page, Andrew and Barbara, can you tell me again when the documents will be ready for transmittal – the overview, the main body of assessment, and appendices. I think we said end of October for the first two? What about the appendices? Once we put this information out there, I would like us to be able to adhere to it. So, can you please confirm?

Other thoughts?

T.

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) < yamada.richard@epa.gov>

**Cc:** Kavlock, Robert < Kavlock.Robert@epa.gov>; Rodan, Bruce < rodan.bruce@epa.gov>;

Orme-Zavaleta, Jennifer <<u>Orme-Zavaleta</u>Jennifer@epa.gov>; Gwinn, Maureen <<u>gwinn.maureen@epa.gov</u>>; Sjogren, Mya <<u>Sjogren.Mya@epa.gov</u>>; Kuhn, Kevin <<u>Kuhn.Kevin@epa.gov</u>>; Fegley, Robert <<u>Fegley.Robert@epa.gov</u>>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Bussard, David

<Bussard.David@epa.gov>

Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday – I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices – Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

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Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile: 2 Ex.6-Personal Privacy | Email: <u>Bahadori, Tina@epa.gov</u>



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 11/2/2017 3:23:28 PM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]; Bateson, Thomas [Bateson.Thomas@epa.gov]; Thayer, Kris

[thayer.kris@epa.gov]

**Subject**: RE: Formaldehyde Science Discussion

I'll meet you at the bus

From: Glenn, Barbara

Sent: Wednesday, November 01, 2017 12:28 PM

To: Bateson, Thomas <Bateson.Thomas@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Kraft, Andrew

<Kraft.Andrew@epa.gov>

Subject: RE: Formaldehyde Science Discussion

# Ex. 5 - Deliberative Process

Then we will discuss anything else Bruce would like.

-Barbara

From: Bateson, Thomas

Sent: Wednesday, November 01, 2017 11:53 AM

To: Thayer, Kris < thayer.kris@epa.gov>; Kraft, Andrew < Kraft.Andrew@epa.gov>; Glenn, Barbara

<Glenn.Barbara@epa.gov>

Subject: RE: Formaldehyde Science Discussion

Consider if it might be useful to cut out the long form section on ML epi.

From: Thaver, Kris

Sent: Wednesday, November 01, 2017 11:51 AM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Bateson, Thomas

<Bateson.Thomas@epa.gov>

Subject: FW: Formaldehyde Science Discussion

I don't think we have any materials, correct

From: Sjogren, Mya

Sent: Wednesday, November 1, 2017 11:29 AM

To: Thayer, Kris <thayer.kris@epa.gov>



**Cc:** Fleming, Megan < <u>Fleming.Megan@epa.gov</u>> **Subject:** RE: Formaldehyde Science Discussion

Hi Kris,

Should we expect materials for this meeting? If so, when might they be available?

Thanks.

Mya Sjogren Immediate Office of the Assistant Administrator Office of Research and Development US EPA (202) 564-2213

----Original Appointment----

From: Rodan, Bruce

Sent: Wednesday, October 25, 2017 8:55 AM

To: Rodan, Bruce; Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming,

Megan

Subject: Formaldehyde Science Discussion

When: Thursday, November 02, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41226 RRB/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

- Barbara Glenn
- Andrew Kraft
- Tom Bateson
- Kris Thayer

At first glance Tuesday 10/31/17 at noon looks good © on everyone's calendar. Hopefully we can snag that soon!!

Thanks,

Tina



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 10/10/2017 1:59:03 PM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]
Subject: RE: Michigan question re formaldehyde

#### Ex. 6 - Personal Privacy

From: Glenn, Barbara

Sent: Tuesday, October 10, 2017 9:30 AM

To: D'Amico, Louis <DAmico.Louis@epa.gov>; Rieth, Susan <Rieth.Susan@epa.gov>; Kraft, Andrew

<Kraft.Andrew@epa.gov>

Cc: Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Rutigliano, Marian

<Rutigliano.Marian@epa.gov>

Subject: RE: Michigan question re formaldehyde

Hey Lou,

I agree this is a question about formaldehyde schedule. We have another request regarding our schedule that we have not as yet answered. So deciding what that answer is would be really good.

Regards, Barbara

From: D'Amico, Louis

**Sent:** Friday, October 06, 2017 1:26 PM **To:** Rieth, Susan <a href="mailto:Rieth.Susan@epa.gov">Rieth.Susan@epa.gov</a>

Cc: Subramaniam, Ravi <<u>Subramaniam.Ravi@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Glenn, Barbara

<<u>Glenn.Barbara@epa.gov</u>>; Rutigliano, Marian <<u>Rutigliano.Marian@epa.gov</u>>

Subject: Re: Michigan question re formaldehyde

Let's touch base on this on Tuesday. The question isn't about historical actions by epa, but the timing of any activity about formaldehyde. Not sure I see the point of sending them copies of older memos.

Lou

(703) 347-0344 (o)

Ex. 6 - Personal Privacy

Sent from my iPhone

(Please pardon brevity and typos)

On Oct 6, 2017, at 12:11 PM, Rieth, Susan < Rieth. Susan@epa.gov > wrote:

Hi Ravi.

FYI, I also forwarded to David, Andrew, and Barbara. Sue

----Original Message-----From: Subramaniam, Ravi

Sent: Friday, October 06, 2017 12:08 PM

To: D'Amico, Louis < <u>DAmico.Louis@epa.gov</u>>



Cc: Bussard, David <<u>Bussard.David@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Rutigliano, Marian <<u>Rutigliano.Marian@epa.gov</u>>; Rieth, Susan <<u>Rieth.Susan@epa.gov</u>> Subject: Michigan question re formaldehyde

Lou:

## Ex. 5 - Deliberative Process

Ravi.

......

Ravi Subramaniam

PYS 11782/ (703) 347-8606 (o), 1 Ex. 6 - Personal Privacy

----Original Message-----From: Rutigliano, Marian

Sent: Friday, October 06, 2017 11:25 AM

To: Subramaniam, Ravi < Subramaniam. Ravi@epa.gov>

Subject: FW: Form submission from: IRIS Contact us about the Integrated Risk Information

System form

----Original Message----

From: King, Bernard

Sent: Friday, October 06, 2017 11:22 AM

To: Radke-Farabaugh, Elizabeth < radke-farabaugh elizabeth@epa.gov >; Rieth, Susan

<Rieth.Susan@epa.gov>; Rutigliano, Marian <Rutigliano.Marian@epa.gov>; Pratt, Margaret

<Soto.Vicki@epa.gov>

Cc: Semeniuk, Michael < Semeniuk. Michael @epa.gov>

Subject: FW: Form submission from: IRIS Contact us about the Integrated Risk Information

System form

**FYI** 

Thank you for contacting the IRIS Hotline.

Sincerely,

Bernard King
IRIS Hotline
EPA Docket Center
Records Information Manager III
Artic Slope Mission Services (ASMS) - Contractor

Phone: (202) 566-1676

Email: king.bernard@epa.gov



----Original Message-----

From: drupal admin [mailto:drupal\_admin@epa.gov]

Sent: Friday, October 06, 2017 11:10 AM

To: IRIS HOTLINE <IRIS HOTLINE@epa.gov>

Subject: Form submission from: IRIS Contact us about the Integrated Risk Information System

form

Submitted on 10/06/2017 11:09AM

Submitted values are:

Name: Dr Divinia Ries Email: <u>riesd@michigan.gov</u>

Comments: We are updating the Michigan cleanup criteria for formaldehyde and initially proposed the use of 2010 IRIS draft's IURF value and the recommendation for mutagenic MOA classification. Due to stakeholder comment, we are now proposing the IRIS 1991 IURF value but retained the MMOA application. Question - Is it likely the final revised or final assessment will be out in 2018? Are you likely changing the MMOA mechanism? Thanks!

Web Area: IRIS



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 10/25/2017 6:56:34 PM

To: Shams, Dahnish [Shams.Dahnish@epa.gov]

**Subject**: Re: do we have a preference for what we are calling IRIS assessment "appendices"?

In the past I could count on it... maybe she's wizening up.

From: Shams, Dahnish

Sent: Wednesday, October 25, 2017 2:55 PM

To: Kraft, Andrew

Subject: RE: do we have a preference for what we are calling IRIS assessment "appendices"?

Does that usually happen? Does Kris always respond?

From: Kraft, Andrew

**Sent:** Wednesday, October 25, 2017 2:54 PM **To:** Shams, Dahnish < Shams. Dahnish@epa.gov>

Subject: Re: do we have a preference for what we are calling IRIS assessment "appendices"?

I'll cover for you this weekend. Thanks for the information, buddy, chin up. [note: it's weird getting responses from people other than Kris when Kris is on the cc line...].

From: Shams, Dahnish

Sent: Wednesday, October 25, 2017 2:52 PM

To: Kraft, Andrew

Subject: RE: do we have a preference for what we are calling IRIS assessment "appendices"?

Don't worry its all gone. I should really start drinking...lol

From: Kraft, Andrew

**Sent:** Wednesday, October 25, 2017 2:51 PM **To:** Shams, Dahnish < <u>Shams. Dahnish@epa.gov</u>>

Subject: Re: do we have a preference for what we are calling IRIS assessment "appendices"?

Nope. Quell your ceaseless optimism.

From: Shams, Dahnish

Sent: Wednesday, October 25, 2017 2:47 PM

**To:** Kraft, Andrew

Subject: RE: do we have a preference for what we are calling IRIS assessment "appendices"?

Yes I did count the letters haha – It's a good thing the overview document is short then  $\odot$ 

I hope this means we get to AR review soon....(FINGERS CROSSED?!)



From: Kraft, Andrew

**Sent:** Wednesday, October 25, 2017 2:47 PM **To:** Shams, Dahnish < Shams. Dahnish@epa.gov>

Subject: Re: do we have a preference for what we are calling IRIS assessment "appendices"?

It is when you call them out about 500000 times!

From: Shams, Dahnish

Sent: Wednesday, October 25, 2017 2:45 PM

**To:** Kraft, Andrew

Subject: RE: do we have a preference for what we are calling IRIS assessment "appendices"?

HA! Appendices is barely shorter!

From: Kraft, Andrew

**Sent:** Wednesday, October 25, 2017 2:42 PM **To:** Shams, Dahnish < Shams. Dahnish@epa.gov >

Cc: Thayer, Kris < thayer.kris@epa.gov>; Glenn, Barbara < Glenn.Barbara@epa.gov>

Subject: Re: do we have a preference for what we are calling IRIS assessment "appendices"?

Sure thing, thanks!

Deliberative Process / Ex. 5

### **Deliberative Process / Ex. 5**

From: Shams, Dahnish

Sent: Wednesday, October 25, 2017 2:36 PM

**To:** Kraft, Andrew **Cc:** Thayer, Kris

Subject: RE: do we have a preference for what we are calling IRIS assessment "appendices"?

I believe in Vicki's most recent template it is called Supplemental Information. Does that answer your question?

- Dahnish

From: Kraft, Andrew

**Sent:** Wednesday, October 25, 2017 1:43 PM **To:** Shams, Dahnish < Shams. Dahnish@epa.gov >

Cc: Thayer, Kris <thayer.kris@epa.gov>

Subject: do we have a preference for what we are calling IRIS assessment "appendices"?

I have seen supplemental materials, supplemental information, and appendices...

Thanks for any clarification.



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 10/25/2017 3:55:17 PM

To: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Bussard, David [Bussard.David@epa.gov]

CC: Glenn, Barbara [Glenn.Barbara@epa.gov]
Subject: Fw: Formaldehyde Science Discussion

FYI. I'm assuming at least Barbara and myself will head over. I think Tom might work remotely on Thursdays.

From: Bahadori, Tina

Sent: Wednesday, October 25, 2017 11:49 AM

To: Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris

Cc: Ross, Mary

Subject: RE: Formaldehyde Science Discussion

This meeting is intended as a focused science discussion just between the four of you with Bruce. I won't participate – neither will David. Should I assume that you will go do the Reagan Building, or do we need video to PYS?

----Original Appointment----

From: Rodan, Bruce

Sent: Wednesday, October 25, 2017 8:55 AM

To: Rodan, Bruce; Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming,

Megan

Subject: Formaldehyde Science Discussion

When: Thursday, November 2, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41226 RRB/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

- Barbara Glenn
- Andrew Kraft
- Tom Bateson
- Kris Thayer

At first glance Tuesday 10/31/17 at noon looks good © on everyone's calendar. Hopefully we can snag that soon!!

Thanks,

Tina



From: Kraft, Andrew [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4A94A4F199B247778ABB02285A51B927-KRAFT, ANDREW]

**Sent**: 11/30/2017 2:33:10 PM

To: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Bussard, David [Bussard.David@epa.gov]

CC: Glenn, Barbara [Glenn.Barbara@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Vulimiri,

Suryanarayana [Vulimiri.Sury@epa.gov]

**Subject**: RE: Hot off the press on Endogenous Formaldehyde

Attachments: formaldehyde\_assessment overview\_IOAAreview\_102617rssvedits.docx; Formaldehyde Main Text

102417rssvEdits.docx

Hi Ravi, good question. It is just too problematic at this point for you to be working in the master versions (on Sharepoint) that Barbara and I are working on.

So, I have attached here a current copy of the main draft and overview documents. Please crosswalk any changes across both documents, and let us know if you also need to make changes to the Appendices (which you can probably work on directly in Sharepoint, as we are not yet working on them).

Since it sounds like you will be working on making changes before Sury, we would prefer if you could make your edits in track changes and then send the docs to Sury, who can then send the docs back to us (or something similar).

#### Thanks!

From: Subramaniam, Ravi

Sent: Thursday, November 30, 2017 9:09 AM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; Bussard, David < Bussard. David@epa.gov>

Cc: Glenn, Barbara <Glenn.Barbara@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Vulimiri,

Suryanarayana < Vulimiri. Sury@epa.gov>

Subject: RE: Hot off the press on Endogenous Formaldehyde

I have set aside some time this morning for formaldehyde, and will add this to my agenda. Ex. 5 - Deliberative Process

### Ex. 5 - Deliberative Process

Andrew, how should I do this (and the other edits I have promised)? Directly, or send you the blurb separately?

Ravi.

Ravi Subramaniam

RRB 51237/ (202) 564-2445 (o) **Ex. 6 - Personal Privacy** 

From: Kraft, Andrew

Sent: Thursday, November 30, 2017 7:56 AM

To: Subramaniam, Ravi < Subramaniam.Ravi@epa.gov >; Bussard, David < Bussard.David@epa.gov >

Cc: Glenn, Barbara < Glenn.Barbara@epa.gov>; Ramasamy, Santhini < Ramasamy.Santhini@epa.gov>; Vulimiri,

Suryanarayana < Vulimiri. Sury@epa.gov>

Subject: RE: Hot off the press on Endogenous Formaldehyde

### Ex. 5 - Deliberative Process

Thanks for sharing, Sury!



From: Subramaniam, Ravi

**Sent:** Thursday, November 30, 2017 7:26 AM **To:** Bussard, David < <u>Bussard.David@epa.gov</u>>

Cc: Kraft, Andrew < Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>

Subject: Re: Hot off the press on Endogenous Formaldehyde

Yes. We have made this point that Sury makes that

When our repair systems don't work for some reason, any endogenous chemical can cause a risk, but the reference and elaboration he gives would help buttress the point. Good!

--Ravi.

\_\_\_\_

Ravi Subramaniam, Ph.D.

Chief, Toxic Effects Branch, IRIS, NCEA, EPA

RRB 51237/ (202) 564-2445 (O) / (Ex. 6 - Personal Privacy m)

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On Nov 30, 2017, at 7:04 AM, Bussard, David < <u>Bussard.David@epa.gov</u>> wrote:

Ravi

This new work - might it be quite relevant to caveats about the Swenberg/Start "bottom up" argument?

David Bussard

Begin forwarded message:

From: "Vulimiri, Suryanarayana" < <u>Vulimiri.Sury@epa.gov</u>>

**Date:** November 29, 2017 at 5:39:41 PM EST **To:** "Bussard, David" < <u>Bussard.David@epa.gov</u>>

Subject: RE: Hot off the press on Endogenous Formaldehyde

David, that is the question I have. It needs some collective thinking into it. Here are some preliminary thoughts.

In the Pontel's paper, which I mentioned earlier, the authors show that there is a problem with endogenous formaldehyde when the ADH5 enzyme (which detoxifies formaldehyde) is absent or when the Fanconi anemia pathway (which repairs crosslink repair) is absent or deficient. They used double knockout mice to show that. So in normal animals, where both these systems are proficient, it should not matter. But people come with catchy titles saying a 'Stem Cell poison' or 'endogenous carcinogen' to divert the attention. When our repair systems don't work for some reason, any endogenous chemical can cause a risk. Another example is that as such we even have tons of endogenous oxidative lesions produced in the body every day, but we are able to repair them and survive. It is a problem with those whose repair systems are flawed for some reason.



Findings from the paper just published (going by abstract) support the established phenomenon about the role of 1C cycle in normal cellular metabolism. Cells convert endogenous formaldehyde to formate which enters the 1C cycle, combines with tetrahydrofolate and after few more steps the 1C units are incorporated into nucleic acid and/or proteins. This is the normal fate of endogenous formaldehyde. We have such in-built scavenging mechanisms or sequestrations in place. The authors also propose an endogenous formaldehyde cycle. But I think this idea was mooted by some earlier researchers. Anyway, don't want to go deep into biochemistry. Dr. Dean Appling from UT Austin, TX would be a good contact who can comment. He is specialized in 1C metabolism. He came for our formaldehyde workshop.

Sury

**Sury Vulimiri, Ph.D., DABT** National Center for Environmental Assessment, Office of Research & Development, US EPA. Phone: 919-541-3558 | Fax: 919-541-0245 | <u>vulimiri.sury@epa.gov</u>

From: Bussard, David

Sent: Wednesday, November 29, 2017 5:06 PM

To: Vulimiri, Suryanarayana < Vulimiri.Sury@epa.gov >

Subject: RE: Hot off the press on Endogenous Formaldehyde

Thanks Sury

What do you think this means for the role of endogenous formaldehyde in assessing the risk of inhaled formaldehyde?

David

Francis Company

From: Vulimiri, Suryanarayana

Sent: Wednesday, November 29, 2017 4:43 PM

To: Bateson, Thomas < Bateson. Thomas@epa.gov>; Glenn, Barbara

<<u>Glenn.Barbara@epa.gov</u>>; Fritz, Jason <<u>Fritz.Jason@epa.gov</u>>; Kraft, Andrew

<<u>Kraft.Andrew@epa.gov</u>>; Makris, Susan <<u>Makris.Susan@epa.gov</u>>; Segal, Deborah

<Segal.Deborah@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>;

Vulimiri, Suryanarayana < Vulimiri.Sury@epa.gov>; Whalan, John

<Whalan.john@epa.gov>

Cc: Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>

Subject: Hot off the press on Endogenous Formaldehyde

Nature. 2017 Aug 31;548(7669):549-554. doi: 10.1038/nature23481. Epub 2017 Aug 16.



### Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism.

Burgos-Barragan G<sup>1</sup>, Wit N<sup>1</sup>, Meiser J<sup>2</sup>, Dingler FA<sup>1</sup>, Pietzke M<sup>2</sup>, Mulderrig L<sup>1</sup>, Pontel LB<sup>1</sup>, Rosado IV<sup>2</sup>, Brewer TF<sup>2</sup>, Cordell RL<sup>2</sup>, Monks PS<sup>2</sup>, Chang CJ<sup>2</sup>, Vazquez A<sup>2</sup>, Patel KJ<sup>2</sup>.

### **Author information**

1

MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge CB2 0QH, UK.

Cancer Research UK Beatson Institute, Glasgow G61 1BD, UK.

3

Instituto de Biomedicina de Sevilla (IBiS) Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, 41013 Seville, Spain.

Λ

Department of Chemistry, Department of Molecular and Cell Biology, and Howard Hughes Medical Institute, University of California, Berkeley, Berkeley, California 94720, USA.

5

Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK.

6

University of Cambridge, Department of Medicine, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.

### Abstract

The folate-driven one-carbon (1C) cycle is a fundamental metabolic hub in cells that enables the synthesis of nucleotides and amino acids and epigenetic modifications. This cycle might also release formaldehyde, a potent protein and DNA crosslinking agent that organisms produce in substantial quantities. Here we show that supplementation with tetrahydrofolate, the essential cofactor of this cycle, and other oxidation-prone folate derivatives kills human, mouse and chicken cells that cannot detoxify formaldehyde or that lack DNA crosslink repair. Notably, formaldehyde is generated from oxidative decomposition of the folate backbone. Furthermore, we find that formaldehyde detoxification in human cells generates formate, and thereby promotes nucleotide synthesis. This supply of 1C units is sufficient to sustain the growth of cells that are unable to use serine, which is the predominant source of 1C units. These findings identify an unexpected source of formaldehyde and, more generally, indicate that the detoxification of this ubiquitous endogenous genotoxin creates a benign 1C unit that can sustain essential metabolism.

PMID: 28813411 DOI: 10.1038/nature23481

<< File: Burgos-Barragan et al 2017\_EndogenouFA.pdf >> << File: Pontel et al 2015 SV.pdf >>

So the bottom line is that endogenous formaldehyde is safely handled by the cells diverting it into normal cellular metabolism. This is published in Nature (PDF attached).

Does this mean there is no need to worry about endogenous formaldehyde for making any adjustments for risk assessment when dealing with exogenous formaldehyde?

One of the co-authors is Pontel, who published earlier an article titled "Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen" in the Journal 'Molecular Cell' on which Dr. Swenberg is a co-author.

MERICAN

Sury

**Sury Vulimiri, Ph.D., DABT** National Center for Environmental Assessment, Office of Research & Development, US EPA. Phone: 919-541-3558 | Fax: 919-541-0245 | <u>vulimiri.sury@epa.gov</u>



#### Message

From: Gentry, Nathan [Gentry.Nathan@epa.gov]

**Sent**: 12/4/2017 5:07:15 PM

To: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Christian, Megan [Christian.Megan@epa.gov]

Subject: RE: Follow-up

I invited Bruce and Richard; I assume Tina should be included as well?

Nathan Gentry

Scheduler for Jennifer Orme-Zavaleta, Richard Yamada, Chris Robbins and Bruce Rodan

**Assistant Deputy Ethics Official** 

EPA Office of Research and Development

Phone: 202-564-9084 Fax: 202-565-2430

From: White, Kimberly [mailto:Kimberly\_White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:51 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Cc: Gentry, Nathan < Gentry. Nathan@epa.gov>

Subject: RE: Follow-up

Great, thank you.

Nathan, feel free to email or give me a call (202-249-6707).

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly\_White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602

www.americanchemistry.com

From: Orme-Zavaleta, Jennifer [mailto:Orme-Zavaleta.Jennifer@epa.gov]

Sent: Monday, December 4, 2017 8:49 AM

**To:** White, Kimberly **Cc:** Gentry, Nathan **Subject:** RE: Follow-up

Thanks for the note and the information. I am cc'ing Nathan Gentry who can follow up with scheduling a time.

Have a good week!

Jennifer Orme-Zavaleta, PhD Principal Deputy Assistant Administrator for Science USEPA Office of Research and Development

Ex. 6 - Personal Privacy

orme-zavaleta.jennifer@epa.gov



From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta.Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21<sup>st</sup> letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22<sup>nd</sup> to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

+++++

<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA<sup>1</sup>, Gentry PR<sup>2</sup>, Dell LD<sup>2</sup>, Rodricks JV<sup>2</sup>, Boffetta P<sup>3</sup>. Author information

Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

#### **KEYWORDS:**

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology

++

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division



Kimberly\_White@americanchemistry.com 700 2<sup>nd</sup> Street NE | Washington, DC | 20002 O: (202) 249-6707 C: (202) 341-7602 www.americanchemistry.com



#### Message

From: White, Kimberly [Kimberly\_White@americanchemistry.com]

**Sent**: 12/4/2017 1:22:13 PM

**To**: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

Subject: Follow-up

Attachments: Mundt et al 2017 - Six Year aftr NRC Review.pdf

Dear Dr. Orme-Zavaleta,

Thank you for your initial response to my November 21<sup>st</sup> letter. Do you have availability for a 1 hour meeting in Washington, DC sometime during the week of January 22<sup>nd</sup> to discuss further?

Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

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<u>Mundt KA</u><sup>1</sup>, <u>Gentry PR</u><sup>2</sup>, <u>Dell LD</u><sup>2</sup>, <u>Rodricks JV</u><sup>2</sup>, <u>Boffetta P</u><sup>3</sup>. **Author information** 

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Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehydecauses leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

### **KEYWORDS:**

Epidemiology; Evidence integration; Hazard evaluation; Mechanistic studies; Regulatory science; Toxicology





### Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly\_White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com



#### Message

From: Wayland, Richard [Wayland.Richard@epa.gov]

**Sent**: 11/7/2017 2:04:06 PM

**To**: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]

Subject: Re: Formaldehyde IRIS review

Will do. Thanks.

Chet

Richard A. "Chet" Wayland Sent from my iPhone

On Nov 7, 2017, at 6:59 AM, Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov > wrote:

Let me know if /when you raise this with your political liaison. It will help on our end navigating with Richard Yamada, who is ours.

Happy to talk if you'd like

Jennifer Orme-Zavaleta, PhD USEPA Office of Research and Development

DC: 202-564-6620 RTP: 919-541-2283 919-699-1564 (cell)

orme-zavaleta.jennifer@epa.gov

From: Sasser, Erika

Sent: Tuesday, November 07, 2017 8:09 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta.Jennifer@epa.gov>

Cc: Wayland, Richard <<u>Wayland.Richard@epa.gov</u>>; Page, Steve <<u>Page.Steve@epa.gov</u>>; Rimer, Kelly <<u>Rimer.Kelly@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>

Subject: Formaldehyde IRIS review

Hi Jennifer-

Recently we have inquired about the status of ORD's review of formaldehyde under the IRIS program, particularly regarding an updated inhalation unit risk estimate. As you know, we have a strong interest in this review and are anxious to see it completed. OAR regularly provides input to ORD on which hazardous air pollutants (HAP) the program office believes may be critical in shaping its regulations, and we have consistently identified formaldehyde as a priority. Having a current cancer unit risk estimate for formaldehyde is critical for the agency's air toxics program, for use in: 1) the National Air Toxics Assessment (NATA), 2) the Clean Air Act (CAA) section 112 risk and technology review (RTR) rulemakings, 3) evaluation of potential risks from on-road and nonroad mobile sources regulated under relevant sections of the CAA, and 4) regional and local-scale risk assessments.

The most recent National Emissions Inventory (NEI Version 1, for emissions year 2014) shows that nationwide, more than 1.3 million tons of formaldehyde are emitted each year. While these emissions are from both natural sources and from stationary and mobile anthropogenic sources,



the inventory estimates that 42,000 industrial facilities emit formaldehyde. The National Air Toxics Assessments (NATA) shows that the entire US population is exposed to formaldehyde.

Formaldehyde has been a pollutant of interest in the RTR program for recently completed reviews and will also be important in upcoming reviews. For RTR source categories already evaluated for remaining risks, formaldehyde was found to be emitted by about one-third. For upcoming RTR rulemakings, we estimate that formaldehyde is emitted by about three-quarters of the source categories.

A current inhalation unit risk for formaldehyde would also be used for current and ongoing risk evaluations for on-road and nonroad mobile sources and for regional and local-scale risk assessments.

We greatly value the rigor of the IRIS program's unit risk evaluations, and we appreciate the intense effort that has already gone into the formaldehyde review. We look forward to updates from ORD as the review progresses.

Thanks, Erika

Erika N. Sasser, Ph.D.
Director, Health and Environmental Impacts Division
Office of Air Quality Planning & Standards, U.S. EPA
109 T.W. Alexander Drive, MD C504-02, RTP, NC 27711
(919) 541-3889 sasser.erika@epa.gov



#### Message

From: Orme-Zavaleta, Jennifer [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3C5A111DC377411595E5B24B5D96146B-ORME-ZAVALETA, JENNIFER]

**Sent**: 12/4/2017 6:54:14 PM

To: Gentry, Nathan [Gentry.Nathan@epa.gov]; Christian, Megan [Christian.Megan@epa.gov]

Subject: RE: Follow-up

yes

Jennifer Orme-Zavaleta, PhD Principal Deputy Assistant Administrator for Science USEPA Office of Research and Development

Ex. 6 - Personal Privacy

orme-zavaleta.jennifer@epa.gov

From: Gentry, Nathan

**Sent:** Monday, December 04, 2017 12:07 PM

To: Orme-Zavaleta, Jennifer <Orme-Zavaleta.Jennifer@epa.gov>; Christian, Megan <Christian.Megan@epa.gov>

Subject: RE: Follow-up

I invited Bruce and Richard; I assume Tina should be included as well?

Nathan Gentry

Scheduler for Jennifer Orme-Zavaleta, Richard Yamada, Chris Robbins and Bruce Rodan

**Assistant Deputy Ethics Official** 

EPA Office of Research and Development

Phone: 202-564-9084 Fax: 202-565-2430

From: White, Kimberly [mailto:Kimberly\_White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:51 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta.Jennifer@epa.gov>

Cc: Gentry, Nathan < Gentry. Nathan@epa.gov>

Subject: RE: Follow-up

Great, thank you.

Nathan, feel free to email or give me a call (202-249-6707).

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com

700 2<sup>nd</sup> Street NE | Washington, DC | 20002 O: (202) 249-6707 C: (202) 341-7602

www.americanchemistry.com

**From:** Orme-Zavaleta, Jennifer [mailto:Orme-Zavaleta.Jennifer@epa.gov]

Sent: Monday, December 4, 2017 8:49 AM



EPA-18-0076-A-000442

**To:** White, Kimberly **Cc:** Gentry, Nathan **Subject:** RE: Follow-up

Thanks for the note and the information. I am cc'ing Nathan Gentry who can follow up with scheduling a time.

Have a good week!

Jennifer Orme-Zavaleta, PhD
Principal Deputy Assistant Administrator for Science
USEPA Office of Research and Development

Ex. 6 - Personal Privacy

orme-zavaleta.jennifer@epa.gov

From: White, Kimberly [mailto:Kimberly White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta.Jennifer@epa.gov>

Subject: Follow-up

Dear Dr. Orme-Zavaleta,

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Separately, I also wanted to alert you to a recently published article by Mundt et al. titled "Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity". I have appended a copy of the in press version to this email and excerpted the abstract below.

<u>Regul Toxicol Pharmacol.</u> 2017 Nov 17. pii: S0273-2300(17)30363-X. doi: 10.1016/j.yrtph.2017.11.006. [Epub ahead of print]

Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity.

Mundt KA<sup>1</sup>, Gentry PR<sup>2</sup>, Dell LD<sup>2</sup>, Rodricks JV<sup>2</sup>, Boffetta P<sup>3</sup>. Author information

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mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

### **KEYWORDS:**

| Epidemiology; | Evidence | integration | n; Hazard ev | aluation; M | echanistic s | tudies; Reg | gulatory scier | nce; Toxicol | logy       |
|---------------|----------|-------------|--------------|-------------|--------------|-------------|----------------|--------------|------------|
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| ++            |          |             |              |             |              |             |                |              |            |
| Kind Regards, |          |             |              |             |              |             |                |              |            |

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
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#### Message

From: Orme-Zavaleta, Jennifer [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3C5A111DC377411595E5B24B5D96146B-ORME-ZAVALETA, JENNIFER]

**Sent**: 12/4/2017 1:49:33 PM

To: Tina Bahadori [Bahadori.Tina@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]

Subject: FW: Follow-up

Attachments: Mundt et al 2017 - Six Year aftr NRC Review.pdf

To start your week...

Jennifer Orme-Zavaleta, PhD
Principal Deputy Assistant Administrator for Science
USEPA Office of Research and Development

Ex. 6 - Personal Privacy

orme-zavaleta.jennifer@epa.gov

From: White, Kimberly [mailto:Kimberly\_White@americanchemistry.com]

Sent: Monday, December 04, 2017 8:22 AM

To: Orme-Zavaleta, Jennifer < Orme-Zavaleta. Jennifer@epa.gov>

Subject: Follow-up

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<u>Mundt KA<sup>1</sup></u>, <u>Gentry PR<sup>2</sup></u>, <u>Dell LD<sup>2</sup></u>, <u>Rodricks JV<sup>2</sup></u>, <u>Boffetta P<sup>3</sup></u>. <u>Author information</u> <u>Abstract</u>

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and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

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|------------------------------------------------------------------------------------------------------------|
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Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly\_White@americanchemistry.com
700 2<sup>nd</sup> Street NE | Washington, DC | 20002
0: (202) 249-6707 C: (202) 341-7602
www.americanchemistry.com



To: Rodan, Bruce[rodan.bruce@epa.gov]; Fleming, Megan[Fleming.Megan@epa.gov]

From: Champlin, Anna

**Sent:** Fri 2/9/2018 4:18:00 PM

Subject: RE: Congressional letter for review

Thanks, Bruce.

Anna (Osaka) Champlin

National Center for Environmental Assessment

EPA Office of Research and Development

(Desk) 202-564-8074

(Cell Ex. 6 - Personal Privacy

From: Rodan, Bruce

Sent: Friday, February 09, 2018 10:08 AM

**To:** Fleming, Megan <Fleming.Megan@epa.gov> **Cc:** Champlin, Anna <Champlin.Anna@epa.gov> **Subject:** RE: Congressional letter for review

Megan, Anna,

Minor comments.

Bruce D. Rodan

Associate Director for Science

U.S. EPA, Office of Research and Development

From: Fleming, Megan



Sent: Thursday, February 8, 2018 11:29 AM To: Rodan, Bruce <<u>rodan.bruce@epa.gov</u>>
Subject: FW: Congressional letter for review

Hi Bruce – This morning we receive this congressional letter from Congressman Graves about the IRIS formaldehyde assessment, along with our draft response. Can you please review and send any comments to me by Friday, or Monday if you need the weekend? It will go to Richard then Jennifer next.

Thanks, Megan

Megan Fleming

Immediate Office of the Assistant Administrator

U.S. EPA Office of Research and Development

1200 Pennsylvania Avenue, N.W.

Washington, D.C. 20460

202-564-6604 (desk), Ex. 6 - Personal Privacy hobile)

From: Champlin, Anna

Sent: Thursday, February 08, 2018 9:23 AM

To: Fleming, Megan < Fleming. Megan@epa.gov >; Christian, Megan

<<u>Christian.Megan@epa.gov</u>>

Subject: Congressional letter for review

Hi MeganF and MeganC,

Not sure if this is the correct procedure to get something to you for review, but attached is a



| letter that we received from Congressman Grav | ves about the IRIS formaldehyde assessment,                          |
|-----------------------------------------------|----------------------------------------------------------------------|
| along with our draft response.                | Ex. 5 - Deliberative Process                                         |
| Ex. 5 - Deliberative Process                  | Ex. 5 - Deliberative Process  Let me know if you need anything else. |
| Thanks,                                       |                                                                      |
| Anna (Osaka) Champlin                         |                                                                      |
| National Center for Environmental Assessmen   | t                                                                    |
| EPA Office of Research and Development        |                                                                      |
| (Desk) 202-564-8074                           |                                                                      |
| (Cell   Ex. 6 - Personal Privacy              |                                                                      |



To: Rodan, Bruce[rodan.bruce@epa.gov]

From: Fleming, Megan

**Sent:** Thur 2/8/2018 5:22:44 PM

Subject: To-do list

Hi Bruce,

Here is my summary of items on your to-do list:

### Ex. 5 - Deliberative Process

- Congressional letter on the IRIS Formaldehyde Assessment and NCEA draft response see email from me on 2/8.
- O Please review and send any comments to me by Monday. (If you need more time, that would



be okay.) Next this goes to Richard then Jennifer.

Thanks,

Megan

Megan Fleming

Immediate Office of the Assistant Administrator

U.S. EPA Office of Research and Development

1200 Pennsylvania Avenue, N.W.

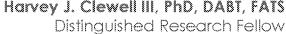
Washington, D.C. 20460

202-564-6604 (desk), Ex. 6 - Personal Privacy Pile)



## Looking Across Data Streams to Draw Conclusions Regarding Causality: Key Considerations in the Formaldehyde Science

October 11-12, 2017









## Potential Value of Different Data Streams



- Animal Bioassays:
  - hazard identification
  - dose-response (in experimental region)
- Epidemiology:
  - human relevance
  - dose-response
- Mechanistic studies:
  - mode of action (mutagenic, cytotoxic, receptor mediated)
  - low-dose extrapolation (linear, nonlinear)
- Modeling:
  - incorporation of mode of action in quantitative risk assessment
  - extrapolation (dose, routes, species)



## Uncertainties in Different Data Streams

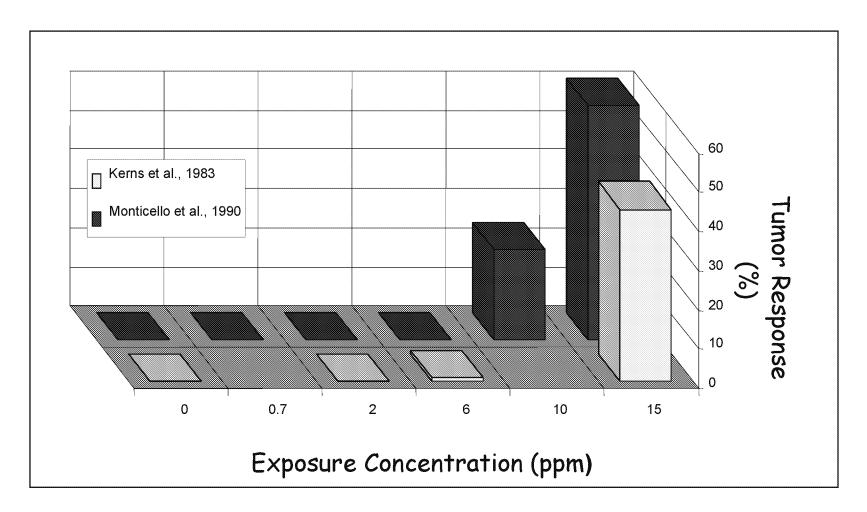


- Animal Bioassays:
  - human relevance
  - dose-response at doses below experimental region
- Epidemiology:
  - impact of confounders, bias (Lash et al. 2012)
  - artificial linearization of dose-response (Crump 2005)
- Mechanistic studies:
  - how to incorporate in quantitative risk assessment
- Modeling:
  - only as good as the data its built on



## Formaldehyde causes nasal tumors in rats...

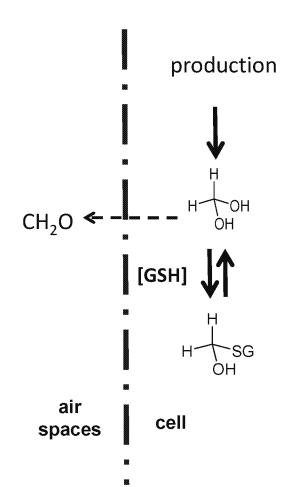






### ...but it's a normal constituent of cells

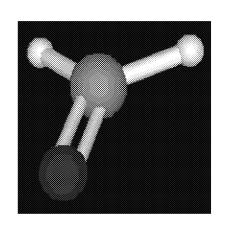


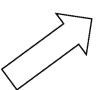


- CH<sub>2</sub>(OH)<sub>2</sub> is formed in cells by metabolism of amino acids and during one carbon pool metabolism.
  - $\bullet$  CH<sub>2</sub>(OH)<sub>2</sub> complexes with glutathione to form hydroxymethylglutathione (K<sub>diss</sub>~ 1.0 mM).
- Total tissue FA in the nasal mucosa in rats, in the absence of any inhalation exposure, was 0.42 ± 0.09 umoles/g (i.e., 12,600 ppb)

## Cancer Risk Assessment Considerations for Formaldehyde

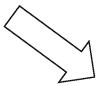




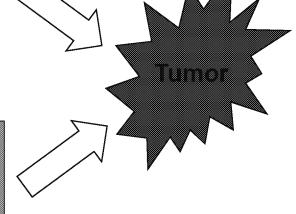


### **DNA** interactions

- DNA-protein cross-links
- DNA mutation?



Increased cell turnover - Due to toxicity



Dosimetry

Modes of action

Effects

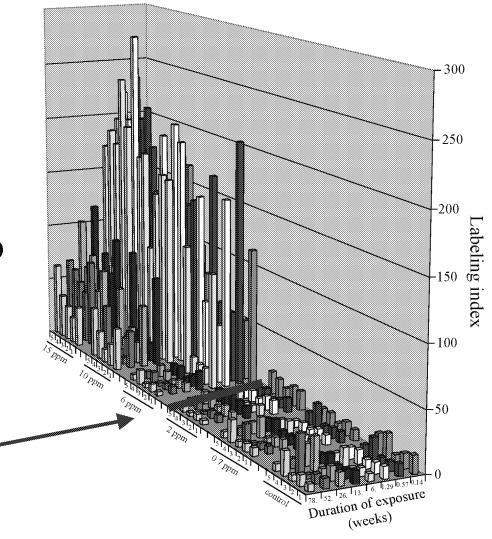


### Cancer mode of action → expected dose/response



 Formaldehyde tumors occur at high inhaled concentrations (above 2 ppm) where severe toxicity leads to increased cell division to replace dead cells

Formaldehyde is a potent irritant; the concentration that reduces breathing rate in mice by 50% (RD50) is 3 ppm





EPA-18-0076-A-000458

## Genomic Markers Changed by Exposures

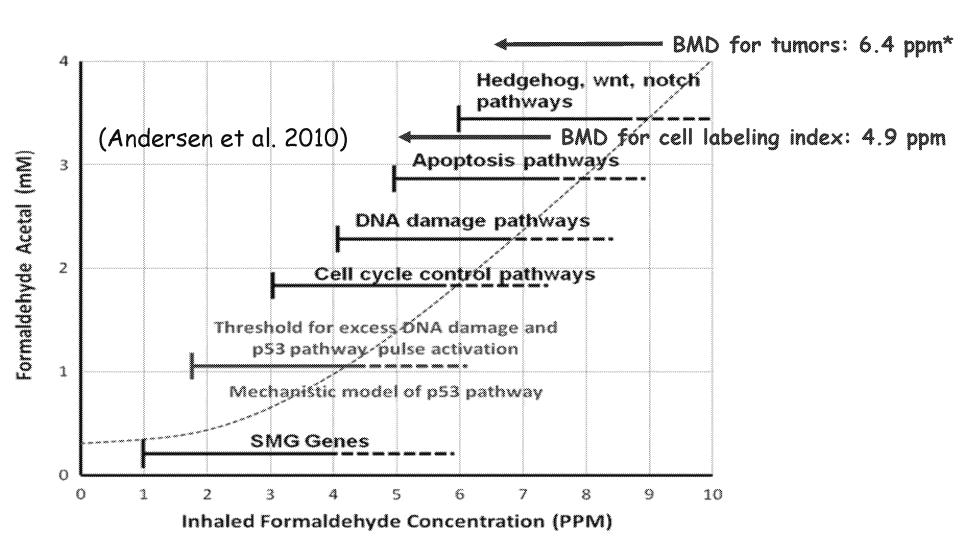


| Sampling<br>Time | 0.7 | 2.0 | 6.0 | 15.0 ppm |  |
|------------------|-----|-----|-----|----------|--|
| 6 hrs            | 0   | 1   | 42  | 773      |  |
| 1 day            | 0   | 0   | 0   |          |  |
| 5 days           | 0   | 15  | 28  |          |  |
| 8 days           | 0   | 0   | 9   |          |  |
| 19 days          | 0   | 0   | 48  |          |  |
| 13 weeks         | 0   | 1   | 116 | 1394     |  |



## Comparison Between Genomic Dose Response and Tumor Response



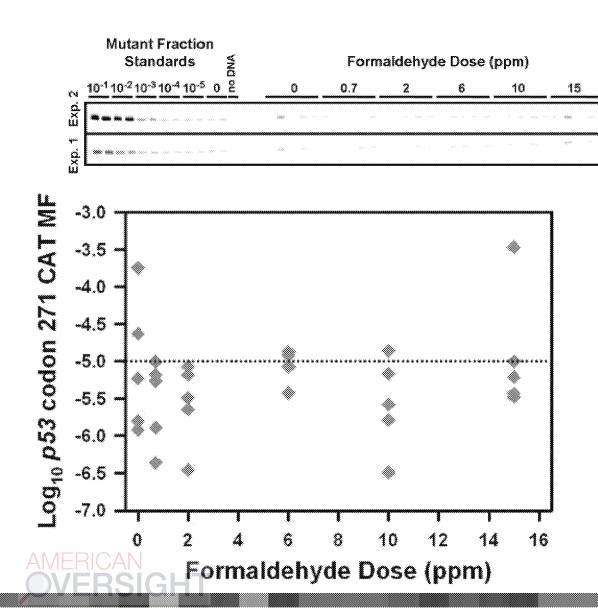




\*(Schlosser, Risk Anal., 2003)

### Analysis of Mutation Frequency in p53 and K-ras Oncogenes





- NCTR analysis
- •Found no increase in p53 or K-ras mutations after 90 days of exposure to formaldehyde at up to 15 ppm
- Demonstrates

   lack of mutagenic
   activity in vivo
   at carcinogenic
   concentrations

EPA-18-0076-A-000461

## NAS Report on the EPA Risk Assessment for Formaldehyde



Endogenous formaldehyde. Humans and other animals produce formaldehyde through various biologic pathways as part of normal metabolism. Thus, formaldehyde is normally present at low concentrations in all tissues, cells, and bodily fluids. Although there is some debate regarding interpretation of the analytic measurements, formaldehyde has been measured in exhaled breath and is most likely present normally at a concentration of a few parts per billion. The endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing the additional dose received by inhalation, particularly at sites beyond the respiratory tract.

Usefulness of various models. Computational fluid dynamics (CFD) models have been developed to help to predict the dose to nasal tissues from inhaled formaldehyde. EPA fairly evaluated the models and sources of uncertainty but did not use the models to extrapolate to low concentrations. The committee concludes that the models would be useful for that purpose and recommends that EPA use the CFD models to extrapolate to low concentrations, include the results in the revised IRIS assessment, and explain clearly its use of CFD modeling approaches.

Given that the BBDR model for formaldehyde is one of the best-developed BBDR models to date, the positive attributes of BBDR models generally, and the limitations of the human data, the committee recommends that EPA use the BBDR model for formaldehyde in its cancer assessment, compare the results with those described in the draft assessment, and discuss the strengths and weaknesses of each approach.



# The presence of endogenous formaldehyde has important low-dose risk assessment implications



### Formaldehyde Wall Mass Flux Predictions on Nonsquamous Epithelium in the Rat, Monkey, and Human Models

| Exposure concentration (ppm) | Rat                                     | Monkey | Human                 |  |  |
|------------------------------|-----------------------------------------|--------|-----------------------|--|--|
|                              | Maximum flux (pmol/(mm <sup>2</sup> h)) |        |                       |  |  |
| 1                            | 9068.9                                  | 8570.2 | 10,183.8              |  |  |
| 0.1                          | 898.6                                   | 870.3  | 1017.1                |  |  |
| 0.01                         | 82.9                                    | 83.4   | 93.1                  |  |  |
| 0.001                        | 1.4                                     | 4.1    | $1.0 \times 10^{-2}$  |  |  |
|                              | Average flux (pmol/(mm <sup>2</sup> h)) |        |                       |  |  |
| 1                            | 503.0                                   | 1680.7 | 1551.2                |  |  |
| 0.1                          | 49.8                                    | 169.4  | 148.8                 |  |  |
| 0.01                         | 4.6                                     | 15.7   | 13.5                  |  |  |
| 0.001                        | 0.1                                     | 0.8    | $-4.0 \times 10^{-2}$ |  |  |



## A simple approach for considering endogenous formaldehyde in a systemic cancer risk assessment (Swenberg et al. 2011)



TABLE 3

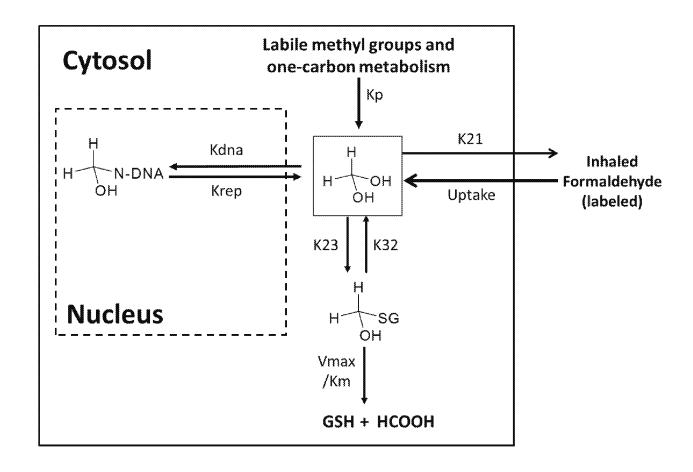
Comparison of Extra Lifetime Risks of Developing NPC, HL, and LEU from Continuous Exposure to 1 ppm Formaldehyde as Estimated Herein Using Formaldehyde-dG Adduct Data (dG-A) from Lu et al. (2010a), Lu et al. (2010b) and Moeller et al. (2011), with Those Estimated by U.S. EPA Using Adult Human Data (Table 6-3, pp. 6-41, 6-42, U.S. EPA draft document)

| Cancer<br>type | Background<br>lifetime risk | Endogenous adducts,<br>mean ± SE<br>(per 10 <sup>7</sup> dG) | UCL <sub>95</sub> slope factor,<br>risk per adduct<br>(per 10 <sup>7</sup> dG) | Exogenous adducts,<br>mean ± SE<br>(per 10 <sup>7</sup> dG) | dG-A UCL <sub>95</sub><br>risk estimate<br>at 1 ppm | EPA UCL <sub>95</sub><br>risk estimate<br>at 1 ppm | Risk ratio,<br>EPA/dG-A |
|----------------|-----------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------|-------------------------|
| NPC            | $7.25 \times 10^{-4}$       | $2.84 \pm 0.51^a$                                            | $3.61 \times 10^{-4}$                                                          | $2.43 \pm 0.29$                                             | $1.22 \times 10^{-3a}$                              | $1.1 \times 10^{-2}$                               | 9.03                    |
|                |                             | $2.63 \pm 0.30^{\circ}$                                      | $3.39 \times 10^{-4}$                                                          | $1.28 \pm 0.17$                                             | $2.18 \times 10^{-3b}$                              |                                                    | 5.05                    |
|                |                             | $4.24 \pm 0.41^{\circ}$                                      | $2.03 \times 10^{-4}$                                                          | $11.15 \pm 1.35$                                            | $7.49 \times 10^{-3}$                               |                                                    | 1.47                    |
|                |                             | $3.41 \pm 0.21^d$                                            | $2.36 \times 10^{-4}$                                                          | $2.03 \pm 0.19$                                             | $2.65 \times 10^{-3d}$                              |                                                    | 4.16                    |
|                |                             | $5.51 \pm 0.53^{\circ}$                                      | $1.56 \times 10^{-4}$                                                          | $1.04 \pm 0.12$                                             | $1.41 \times 10^{-3e}$                              |                                                    | 7.81                    |
|                |                             | $6.09 \pm 1.52^{f}$                                          | $2.02 \times 10^{-4}$                                                          | $0.19 \pm 0.040$                                            | $0.96 \times 10^{-3f}$                              |                                                    | 11.4                    |
|                |                             | $3.62 \pm 0.77^{8}$                                          | $3.08 \times 10^{-4}$                                                          | $0.039 \pm 0.011$                                           | $0.86 \times 10^{-3g}$                              |                                                    | 12.8                    |
|                |                             | $2.05 \pm 0.27^{h}$                                          | $4.50 \times 10^{-4}$                                                          | $0.41 \pm 0.025$                                            | $0.39 \times 10^{-3k}$                              |                                                    | 28.5                    |
|                |                             | $2.49 \pm 0.23^{i}$                                          | $3.42 \times 10^{-4}$                                                          | 0.25 ± 0.020                                                | $0.54 \times 10^{-3i}$                              |                                                    | 20.5                    |
| HL             | $2.3 \times 10^{-3}$        | $1.10 \pm 0.16^a$                                            | $2.76 \times 10^{-3}$                                                          | $< 1.77 \times 10^{-2j}$                                    | $< 6.78 \times 10^{-3j}$                            | $1.7 \times 10^{-3}$                               | > 251                   |
|                |                             | $1.29 \pm 0.19^{b}$                                          | $2.36 \times 10^{-3}$                                                          | $< 1.77 \times 10^{-2i}$                                    | $< 20.9 \times 10^{-5j}$                            |                                                    | > 81.2                  |
| LEU            | $1.3 \times 10^{-2}$        | $1.17 \pm 0.20^{a}$                                          | $1.55 \times 10^{-2}$                                                          | $< 1.77 \times 10^{-2j}$                                    | < 3.81 × 10 <sup>-4j</sup>                          | $5.7 \times 10^{-2}$                               | > 149.4                 |
|                |                             | 1.05 ± 0.081 <sup>b</sup>                                    | $1.42 \times 10^{-2}$                                                          | < 1.77 × 10 <sup>2j</sup>                                   | < 12.6 × 10 <sup>-4</sup> /                         |                                                    | > 45.2                  |
|                |                             | $12.4 \pm 1.82^{h}$                                          | $1.38 \times 10^{-3}$                                                          | $< 1.03 \times 10^{-3k}$                                    | $< 2.96 \times 10^{-6k}$                            |                                                    | > 19,256                |
| AMEF           | RICAN                       | $17.5 \pm 1.31'$                                             | $0.85 \times 10^{-3}$                                                          | $< 1.03 \times 10^{-3k}$                                    | $< 5.47 \times 10^{-6k}$                            |                                                    | > 10,420                |

EPA-18-0076-A-000464

## A pharmacokinetic model that includes endogenous formaldehyde is now available for inclusion in the CIIT BBDR model

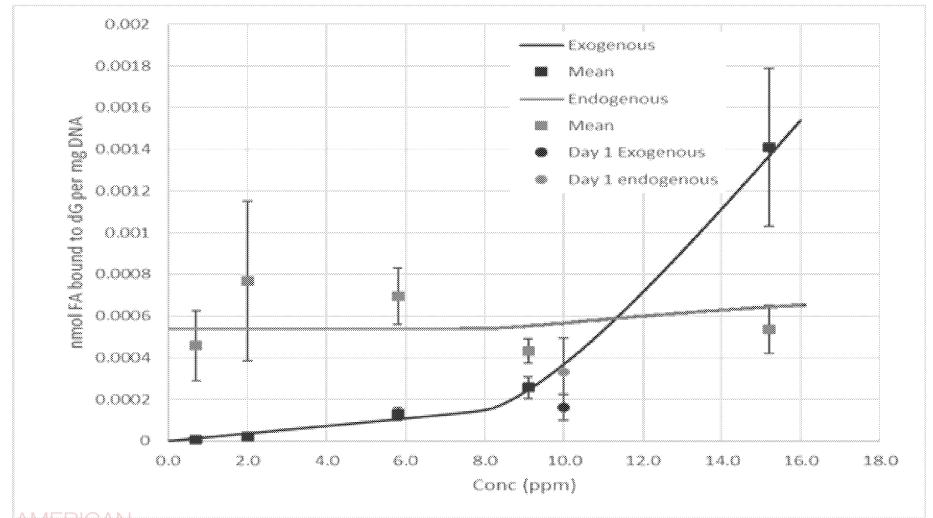






Endogenous and exogenous formaldehyde binding to dG in rat nasal tissue after a single 6-hour exposure to labelled formaldehyde concentrations of 1, 2, 6, 9, 10, and 15 ppm.

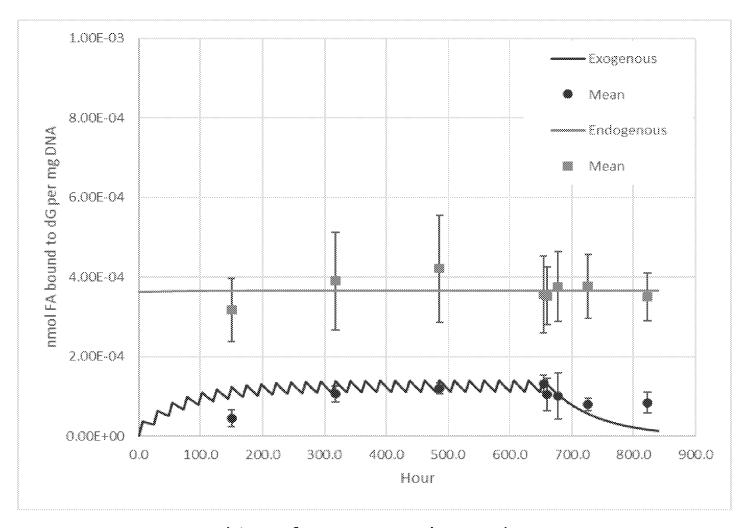




(circles: data from Lu et al. 2010; squares: data from Luetal, 2011)

Endogenous (green) and exogenous (red) dG binding of formaldehyde in rat nasal tissue from exposure to 2 ppm formaldehyde 6 hours per day, 7 days per week, for 28 days.



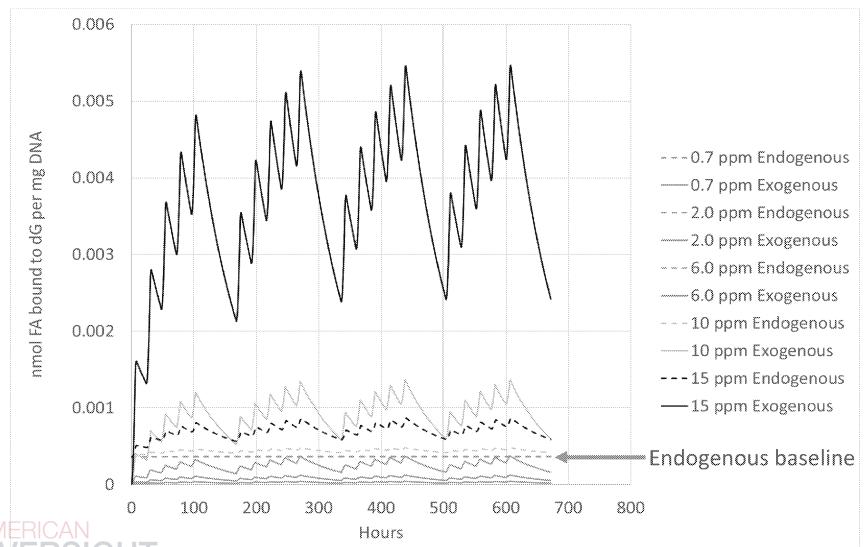




(data from Yu et al. 2015)

Model-predicted endogenous (dashed lines) and exogenous (solid lines) formaldehyde-dG adducts at the exposure concentrations used in the 2-year inhalation bioassays in the rat (Kerns et al. 1983, Monticello et al. 1996)

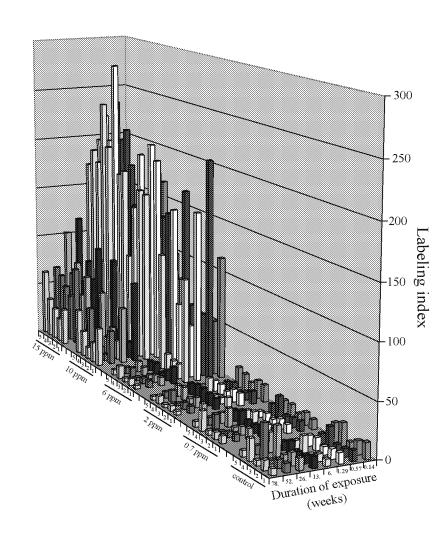




#### Conclusions

Scito Vation INNOVATIVE CELL BASED SCIENCE

- Genomic analysis shows that tumors occur at concentrations associated with severe cellular disruption (6 ppm and above)
- Mutation analysis shows no evidence of mutagenic activity at concentrations that are clearly toxic and tumorigenic
- Modeling of endogenous and exogenous DNA adduct data supports a nonlinear dosedependence
- These mechanistic studies provide support for a threshold for formaldehyde carcinogenicity



EPA-18-0076-A-000469

# Summary of Global Risk Assessment Approaches for the Formaldehyde Science – General Approaches of the EU, Canada, WHO and the US

James S. Bus PhD DABT ATS

Exponent, Inc.

Formaldehyde Science Invited Experts Workshop:

Understanding Potential Human Health Cancer Risk – From Data Integration to Risk Evaluation

October 10-11, 2017, Chapel Hill, NC



#### EU – ECHA (2012) Hazard/Risk Classification

- Carc 1B (H350): "May cause cancer"; "limited" human (NPC only); "sufficient" animals (NPC);
- Muta 2 (H341): "suspected of causing genetic defects"
- "Suspected germ cell mutagen" due to site of contact DPX genotoxicity
- "No convincing evidence of a carcinogenic effect at distant sites or via routes of exposure other than inhalation."
- Mode of Action:
  - "Common understanding formaldehyde causes tumors above a threshold concentration by mechanisms that are initiated by the cytotoxic effects and secondarily regenerative cell proliferation", ...but
  - "...data does not allow firm conclusion on a threshold-mode of action"



#### **WHO**

- WHO/IPCS CICADS (Concise International Assessment Document; 2002)
  - Animal/human cancer: Only respiratory tract tumors fulfill causality criteria
  - Mode of Action: Carcinogenic hazard to humans "...under conditions that induce cytotoxicity and sustained proliferation."
  - Moderate to high confidence in data indicating an "obligatory role of regenerative proliferation" for nasal tumors, although mechanism is unclear.
- WHO IARC (2012)
  - Classification 1 "Carcinogenic to humans" "Sufficient" evidence in humans and animals (NPC); "small majority" for "sufficient" evidence of leukemias
  - Mode of Action: Cell replication in response to cytotoxicity promotes carcinogenicity; assumed genotoxic – "moderately supports" leukemias



#### Canada

- Priority Substances List Assessment Report (2001)
  - CEPA Schedule 1 "toxic"
  - DSL Low priority substance (already risk managed; risks below Canada population-level exposures)
  - Carcinogenic hazard to humans "...under conditions that induce cytotoxicity and sustained regenerative cell proliferation."
    - Genotoxicity cannot be excluded as contributing mechansism
- Health based guidance value (2004)
  - Predicted risk at chronic exposure to 1.2 ppb = 2.3 X 10<sup>-10</sup>



#### **United States**

- EPA IRIS, under revision
  - Sufficient evidence of causal association for NPC, all leukemias, myeloid leukemia and LHP as group in humans
  - Animals data provide strong support for NPC, but limited data for LHP cancers
  - For NPC, mutagenic MoA operating in conjunction with key event of formaldehyde cytotoxicity-induced cell proliferation
  - Lifetime cancer risk at 1 ppb =  $1 \times 10^{-4}$
- NTP Report on Carcinogens (2011)
  - "Known to be a human carcinogen"
  - Sufficient evidence in humans: nasal and myeloid leukemias
  - Sufficient evidence in animals: multiple species, sites and routes
  - Mechanistic events plausible in humans, including genotoxicity



#### Occupational Exposure Assessments

- German MAK: 0.3 ppm TWA, momentary value of 1 ppm
  - Cancer classification 4: non-genotoxic; cell proliferation important to MoA
- SCOEL: 0.3 ppm TWA, 0.6 ppm STEL
  - Cancer classification Group C: genotoxic carcinogen with a MoA-based threshold
- ACGIH: 0.1 ppm TWA, 0.3 ppm STEL
  - Cancer classification A1: confirmed human carcinogen
- NIOSH: 0.016 ppm REL, 0.1 ppm STEL
  - Cancer classification: carcinogen
- OSHA: 0.75 ppm TWA, 2 ppm STEL
  - Cancer classification: potential to cause cancer



## Mode of Action: Cytotoxicity causing regenerative cell proliferation in upper respiratory tract consistently identified

- Current MoA evaluations focused entirely on formaldehyde
- Little consideration of toxicity and carcinogenicity associated with chemicals extensively systemically metabolized to formaldehyde, and how such data might further inform the MoA
  - Methyl chloride
    - Weak male mouse carcinogen; non-carcinogen in rats
    - Liver, brain, and testis formaldehyde increased after inhalation exposure
    - Depletes glutathione, a key detoxification mechanism
  - Caffeine
    - Extensively demethylated to formaldehyde; daily 400 mg dose of caffeine liberates approximately 2 mmoles of formaldehyde (60 mg)



#### **FORMALDEHYDE**

## Understanding Potential Human Cancer Risk: From Data Integration to Risk Evaluation

# Workshop Purpose and Objectives

Kenneth A. Mundt, PhD, FACE
Ramboll Environ
Formaldehyde Science Invited Experts Workshop
October 10-11, 2017



## IRIS Workshop on Formaldehyde *April 2014*

#### The workshop focused on three themes:

- The influence of endogenous formaldehyde on the toxicity of inhaled formaldehyde, and implications for the health assessment;
- Mechanistic evidence relevant to inhaled formaldehyde and lymphohematopoietic cancers (leukemia and lymphomas); and
- Epidemiological research on formaldehyde exposure and lymphohematopoietic cancers (leukemia and lymphomas).



## IRIS Workshop on Formaldehyde *April 2014*

The overarching goal of the EPA workshop:

"To facilitate scientific discussion of these topics and the scientific challenges they pose for assessing the health hazards of inhaling formaldehyde."

https://www.epa.gov/iris/formaldehyde-workshop



### Today's Workshop: Purpose

Collaboration
Discussion
Innovation
Understanding

To provide a broadly collaborative opportunity to develop innovative approaches to integrating toxicological, mechanistic and epidemiological evidence and understanding their contributions to scientifically sound risk assessments.



#### Today's Workshop: Objectives

Review
Integration
Causality
Data gaps
Risk Assessment

Review major lines of evidence on formaldehyde exposure and cancers.

Explore approaches to integrating evidence to reach causal conclusions.

Identify data requirements and gaps regarding cancer hazard and risk assessment.

Define key health endpoints and frameworks for objective risk assessment.



### Enjoy the Workshop!



# Key Events and Considerations for LHP Cancers

Kenneth A. Mundt, PhD, FACE
Ramboll Environ
Formaldehyde Science Invited Experts Workshop
October 10-11, 2017



## Evaluations of Formaldehyde and LHP Cancers

Over the last 13 years, several formaldehyde evaluations have been performed (year finalized), including the following:

- 2004: IARC Monograph 88 (2006)
- 2009: IARC Monograph 100F (2012)
- 2010: EPA DRAFT IRIS Toxicological Review (pending)
- 2012: NTP 12<sup>th</sup> Report on Carcinogens (2013)
- 2016: Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL) (2016)



#### 2004: IARC (Monograph 88, 2006)

Classification: Carcinogenic to humans (Group 1)

Epidemiological evidence: Sufficient, based on nasopharyngeal

cancer

Leukemia: "There is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers." (p.276)



### 2004: IARC (Monograph 88, 2006)

**Supporting data:** Mechanism for inducing myeloid leukema is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells.

"The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukaemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans." (p. 280)



### 2009: IARC Monograph 100F (2012)

Classification: Carcinogenic to humans (Group 1)(unchanged) Epidemiological evidence: Formaldehyde causes cancer of the nasopharynx and leukaemia.

"The Working Group was not in full agreement on the evaluation of formaldehyde causing leukaemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited." (p. 430)



### 2009: IARC Monograph 100F (2012)

**Toxicological evidence:** "Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427)

"Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p.428)

"Inconsistent genotoxic effects [seen] in blood lymphocytes from animals exposed to formaldehyde via inhalation."



### 2009: IARC Monograph 100F (2012)

**Supporting data:** "Particularly relevant. . was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukeaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological prescursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430)

"Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans." (p. 430)



**Epidemiological evidence:** "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (page 6-46).



All LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts (embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (page 4-180).



**All leukemias combined:** "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group." (page 4-182)



**Toxicological evidence:** Limited evidence to support conclusion that formaldehyde exposure causes leukemia. Four studies evaluated the leukemic potential of formaldehyde.

"Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after chronic inhalation exposures (Sellakumar et al., 1985)." (p.6-21)



Supporting data: "Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been docoumented in formaldehyde exposed workers, including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells." (p.6-22)



#### 2012 NTP 12th RoC (2013)

**Epidemiological evidence:** "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans.

Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding.

The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia." (p. 195) (continued)



#### 2012 NTP 12th RoC (2013)

**Toxicological evidence:** "Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these turmos were exposure-related, because of limitations in the reporting of these tumors (Soffritti et al., 2002)." (p. 198)



#### 2012 NTP 12th RoC (2013)

**Supporting data:** "Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves 2004)."

"Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al. 2010a)."

"Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites." (p. 199)



## 2012: European Chemicals Agency (ECHA), Committee for Risk Assessment (RAC) (2012)

Classification: Carcinogen 1B - H50 f (May cause cancer)

**Epidemiological evidence:** "In conclusion, while some studies have found increased rates of leukaemia, the epidemiology data do not show consistent findings across studies for leukaemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates."

"Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukaemia." (p.41)

(continued)
MERICAN
VERSIGHT

## 2012: European Chemicals Agency (ECHA), Committee for Risk Assessment (RAC) (2012)

**Toxicological evidence:** "No indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumours in inhalation study of rats and mice (Kerns et al. 1983)." (p.22)

**Supporting data**: "Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations."

"These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the port of entry." (p.44)



# 2016: Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL, 2016)

**Epidemiological evidence:** "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45)



# 2016: Scientific Committee on Occupational Exposure Limits for Formaldehyde (SCOEL, 2016)

**Toxicological Evidence:** "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49)

**Supporting Data:** "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49)



#### **Additional Considerations**

- Science evolves, and the scientific landscape today is different from 10 years or more ago
- Where do differences persist, and why?
- Are there data gaps? Can we identify practical ways of filling them?
- If formaldehyde is/is not leukemogenic, what is the best framework for risk assessment?



## Thank you.



# Understanding the Formaldehyde Science and Putting the Puzzle Pieces Together – Integrating New Science into Risk Evaluation Processes

Robinan Gentry, PhD, DABT
Ramboll Environ
Formaldehyde Science Invited Experts Workshop
October 10, 2017



#### **Hazard Characterization**

# Conclusions regarding formaldehyde carcinogenicity

- Regulatory Conclusions inconsistencies between EPA, ECHA, WHO, IARC, and NTP regarding the potential carcinogenicity of formaldehyde
- Diseases of Concern nasopharygeal (NPC) and all lymphohematopoietic (LHP) cancers
  - Some focus by selected agencies on the specific diseases - Acute Myeloid Leukemia (AML)
- NPC specific questions the potential for a threshold and rarity of the tumor
- LHP specific questions the biological plausibility of formaldehyde exposure causing all LHP cancers versus specific subtypes



#### **Hazard Characterization**

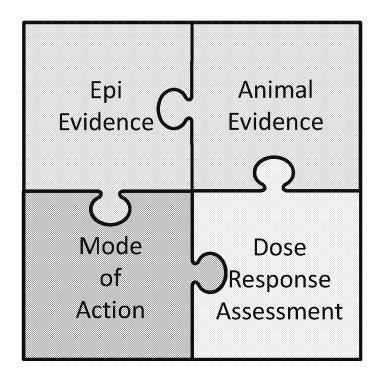
## Conclusions regarding formaldehyde carcinogenicity

#### Approaches to discuss:

- Systematic Review protocol development, evidence identification, evidence evaluation, analytic summary of the evidence
- Weight of Evidence a summary, considering both the quality and quantity of data to support conclusions regarding human carcinogenic potential
- Evidence Integration qualitative or quantitative approaches to integrate multiple streams of evidence to reach determinations of whether or not the evidence is adequate to draw conclusions related to potential hazard and causality
- Mode of action (MOA) frameworks evaluation of the available mechanistic or mode of action data in a systematic way to determine which proposed MOAs are supported by the available evidence and support causality and relevance to humans



## Integration of Evidence and Determination of Causality

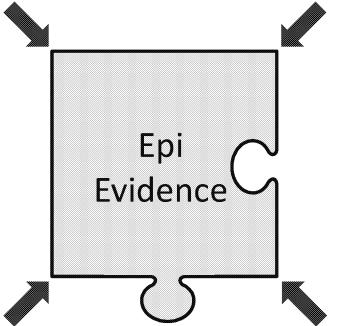




## NPC – Epidemiological

Evidence of upper respiratory cancer versus other sites

Defining the strengths, weaknesses, and inconsistencies of key studies

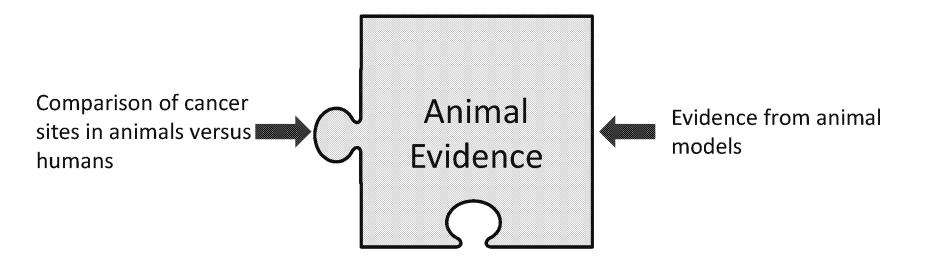


Statistical power of studies, given rarity of cancer

Selection of studies for dose-response modeling



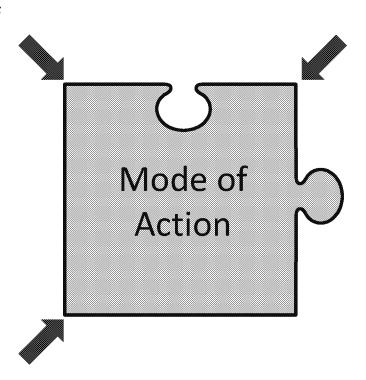
## **NPC - Animal**





#### NPC - Mode of Action

Understanding the role of endogenous formaldehyde



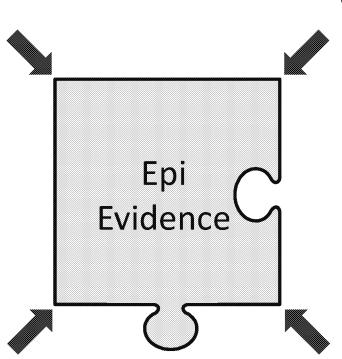
Role of mutagenicity and cytotoxicity

Potential for a threshold



## LHP - Epidemiological

Specific versus grouped LHM cancers



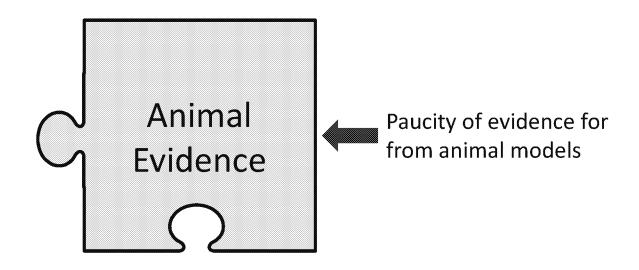
Defining the strengths, weaknesses, and inconsistencies of key studies

Understanding non-traditional exposure metrics

Selection of studies for dose-response modeling



## LHP - Animal





### LHP - Mode of Action

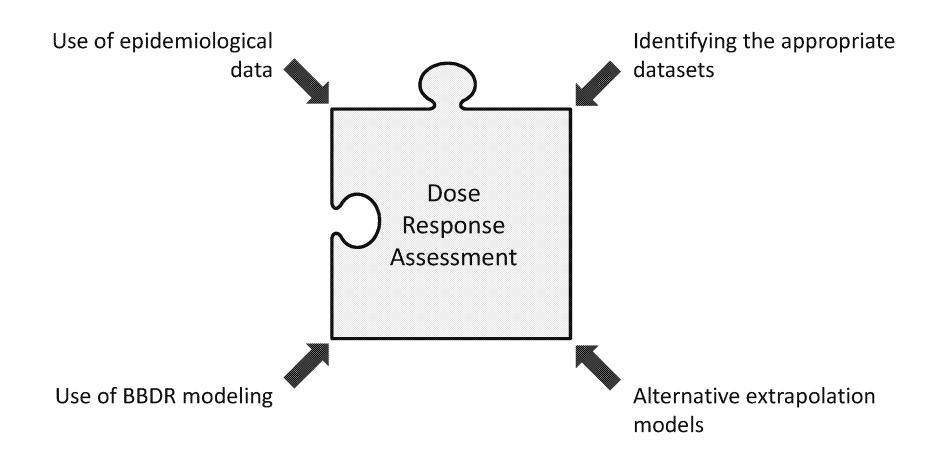
Reconciling divergent Understanding the role of statements regarding endogenous formaldehyde systemic delivery Mode of Action Reconciling varying Data regarding potential for an euploidy/cytogenetic conclusions regarding



causality

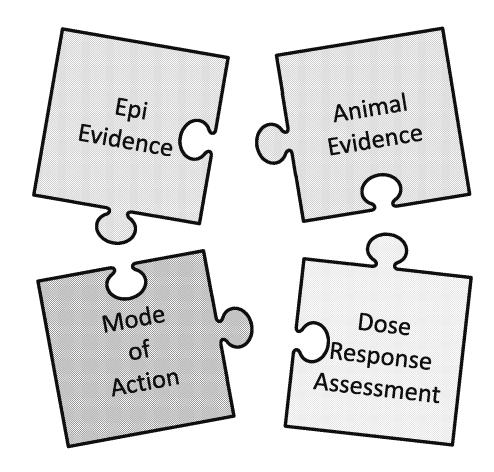
effects at distant sites

## Quantitative Analyses for Cancer





## Putting the pieces together



How do we set up the framework for conducting a risk assessment for formaldehyde integrating the best available science and methods?



#### Message

From: Rodan, Bruce [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=RODAN, BRUCE]

**Sent**: 2/9/2018 3:07:31 PM

To: Fleming, Megan [Fleming.Megan@epa.gov]
CC: Champlin, Anna [Champlin.Anna@epa.gov]

**Subject**: RE: Congressional letter for review

Attachments: Graves formaldehyde letter\_v2 (003).docx

Megan, Anna,

Minor comments.

Bruce D. Rodan
Associate Director for Science
U.S. EPA, Office of Research and Development

From: Fleming, Megan

**Sent:** Thursday, February 8, 2018 11:29 AM **To:** Rodan, Bruce <rodan.bruce@epa.gov> **Subject:** FW: Congressional letter for review

Hi Bruce – This morning we receive this congressional letter from Congressman Graves about the IRIS formaldehyde assessment, along with our draft response. Can you please review and send any comments to me by Friday, or Monday if you need the weekend? It will go to Richard then Jennifer next.

Thanks, Megan

Megan Fleming
Immediate Office of the Assistant Administrator
U.S. EPA Office of Research and Development
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460
202-564-6604 (desk), 2 Ex. 6 - Personal Privacy (mobile)

From: Champlin, Anna

Sent: Thursday, February 08, 2018 9:23 AM

To: Fleming, Megan <Fleming.Megan@epa.gov>; Christian, Megan <Christian.Megan@epa.gov>

Subject: Congressional letter for review

Hi MeganF and MeganC,

Not sure if this is the correct procedure to get something to you for review, but attached is a letter that we received from Congressman Graves about the IRIS formaldehyde assessment, along with our draft response. Currently, Tina's signature line is on the draft, but may be more appropriate for Jennifer to sign. Up to you guys. Let me know if you need anything else.

Thanks,

Anna (Osaka) Champlin



National Center for Environmental Assessment EPA Office of Research and Development (Desk) 202-564-8074 (Cell) Ex. 6 - Personal Privacy



| Chemical                                 | CASEN      | RIS Assessment Lead |
|------------------------------------------|------------|---------------------|
| Ammonia- oral                            | 7664-41-7  | Vince Cogliano      |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Arsenic, inorganic - oral and inhalation | 7440-38-2  | Janice Lee          |
| Chloroform- inhalation                   | 67-66-3    | Ted Berner          |
| Chloroform- inhalation                   | 67-66-3    | Ted Berner          |
| Chloroform- inhalation                   | 67-66-3    | Ted Berner          |
| Chromium VI- inhalation                  | 18540-29-9 | Catherine Gibbons   |
| Chromium VI- inhalation                  | 18540-29-9 | Catherine Gibbons   |
| Chromium VI- inhalation                  | 18540-29-9 | Catherine Gibbons   |
| ETBE- oral                               | 637-92-3   | Keith Salazar       |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Ethylbenzene- oral and inhalation        | 100-41-4   | Paul Reinhardt      |
|                                          |            | George Woodall      |
| Formaldehyde- oral                       | 50-00-0    | Barbara Glenn       |
|                                          |            | Andrew Kraft        |
| HBCD                                     | 3194-55-6  | Laura Dishaw        |
|                                          |            | April Luke          |
| HBCD                                     | 3194-55-6  | Laura Dishaw        |
|                                          |            | April Luke          |
| Manganese- inhalation                    | 7439-96-5  | Ila Cote            |
| Manganese- inhalation                    | 7439-96-5  | Ila Cote            |



#### **IRIS Chemical Patrons Information**

| Patron Requesting Offices | Patron P®€        | Patron Contact Information |
|---------------------------|-------------------|----------------------------|
| OW                        | Greg Miller       | 202-566-2310               |
| ATSDR                     | Selene Chou       | 770-488-3357               |
| FDA                       | Suzie Fitzpatrick | 240-402-3042               |
| HealthCanada              | Scott Blechinger  | 613-948-2018               |
| OAR                       | Bob Hetes and     | 919-541-1589               |
|                           | Deirdre Murphy    | 919-541-0729               |
| OLEM                      | Stiven Foster and | 202-566-1911               |
|                           | Kathleen Raffaele | 202-566-0301               |
| OP                        | Dan Axelrad       | 202-566-2304               |
| OPP                       | Garland Waleko    | 703-308-8049               |
| OW                        | Greg Miller,      | 202-566-2310               |
|                           | Tanja Crk,        | 202-566-1037               |
|                           | Erica Fleisig,    | 202-566-1057               |
|                           | John Healey       | 202-566-0176               |
| OAR                       | Amy Vasu          | 919-541-0107               |
| OLEM                      | Rich Kapuscinski  | 703-305-7411               |
| Region 4                  | Glenn Adams       | 404-562-8771               |
| OW                        | Greg Miller       | 202-566-2310               |
| Region 7                  | Mike Beringer     | 913-551-7351               |
| Region 10                 | Julie Wroble      | 206-553-1079               |
| OTAQ-OAR                  | BEEN NO CONTACT   |                            |
| OAR                       | Amy Vasu          | 919-541-0107               |
| OLEM                      | Stiven Foster and | 202-566-1911               |
|                           | Kathleen Raffaele | 202-566-0301               |
| OW                        | Greg Miller       | 202-566-2310               |
| Region 1                  | Meghan Cassidy    | 617-918-1387               |
|                           | og.iai. cassia,   |                            |
| Region 2                  | Marian Olsen      | 212-637-4313               |
| Region 4                  | Glenn Adams       | 404-562-8771               |
| OAR                       |                   |                            |
| OP                        | Dan Alexrad       | 202-566-2304               |
| OPPT                      | Iris Camacho      | 202-564-1229               |
| OAQPS-OAR                 | Amy Vasu          | 919-541-0107               |
| 0,100,00,00               |                   |                            |



| OW's nur              | nber 3 priori | ity on 2014         |                                         |
|-----------------------|---------------|---------------------|-----------------------------------------|
|                       | -             | 1                   |                                         |
|                       |               |                     |                                         |
|                       |               |                     |                                         |
|                       |               |                     |                                         |
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|                       |               |                     |                                         |
|                       |               |                     |                                         |
|                       |               |                     |                                         |
|                       |               |                     |                                         |
| OW's nur              | nber one pri  | ority based on 2014 | 1                                       |
| Also inte             | rested: CalEl | PA, NJ DEP, NC DEC  | <b>l</b>                                |
| Marc Stife<br>Uranium | elman nas pe  | een contact for R10 | for                                     |
| Janice Le             |               |                     | *************************************** |
| Juliec Ec.            | 9             |                     |                                         |
| Juliec Ec             | 2             |                     |                                         |
| James Ec.             | 2             |                     |                                         |
| Jamee Ec.             | 2             |                     |                                         |
| June Ec               | 2             |                     |                                         |
|                       | 2             |                     |                                         |
|                       | 2             |                     |                                         |
|                       | 2             |                     |                                         |
|                       |               | iority on 2014      |                                         |



| Manganese- inhalation            | 7439-96-5                | lla Cote                      |
|----------------------------------|--------------------------|-------------------------------|
| Manganese- inhalation            | 7439-96-5                | Ila Cote                      |
| МеНд                             | 22967-92-6               | Deb Segal                     |
| МеНд                             | 22967-92-6               | Deb Segal                     |
| МеHg                             | 22967-92-6               | Deb Segal                     |
| Mercury Salts                    |                          | Jason Fritz                   |
| Naphthalene- oral and inhalation | 91-20-3                  | Ingrid Druwe                  |
| Naphthalene- oral and inhalation | 91-20-3                  | Ingrid Druwe                  |
| Naphthalene- oral and inhalation | 91-20-3                  | Ingrid Druwe                  |
| Naphthalene- oral and inhalation | 91-20-3                  | Ingrid Druwe                  |
| Nitrate/Nitrite- oral            | 14797-55-8               | Larissa Pardo                 |
|                                  | 14797-65-0               |                               |
| Nitrate/Nitrite- oral            | 14797-55-8<br>14797-65-0 | Larissa Pardo                 |
| PAH PRFs                         |                          | Karen Hogan<br>Margaret Pratt |
| PCBs- oral                       | 1336-36-3                |                               |
| PCBs- oral                       | 1336-36-3                | Geniece Lehmann               |
| PCBs- oral                       | 1336-36-3                | Geniece Lehmann               |
| RDX- oral                        | 121-82-4                 | Lou D'Amico                   |
| tert-Butanol                     | 75-65-0                  | Janice Lee                    |
| Uranium- oral                    | 7440-61-1                | Paul White                    |
| Uranium- oral                    | 7440-61-1                | Paul White                    |



| OLEM                    | Stiven Foster and           | 202-566-1911 |
|-------------------------|-----------------------------|--------------|
|                         | Kathleen Raffaele           | 202-566-0301 |
| Region 5                | Carole Braverman            | 312-353-7359 |
| OAR                     | Amy Vasu                    | 919-541-0107 |
| ОСНР                    | Rebecca Dzubow              | 202-564-0967 |
|                         | and Sue Euling              | 202-566-2717 |
| OW                      | Greg Miller                 | 202-566-2310 |
| OLEM                    | Stiven Foster               | 202-566-1911 |
|                         | Kathleen Raffaele           | 202-566-0301 |
|                         | Antonio Yaquian-Luna (Jose) | CANNOT FIND  |
| OAR                     | Amy Vasu                    | 919-541-0107 |
| ОСНР                    | Sue Euling                  | 202-566-2717 |
| OLEM/Regional Superfund | Stiven Foster and           | 202-566-1911 |
|                         | Kathleen Raffaele           | 202-566-0301 |
|                         | Meghan Cassidy              | 617-918-1387 |
|                         | Marian Olsen                | 212-637-4313 |
|                         | Mario Mangino               | 312-886-2589 |
|                         | Kelly Schumacher            | 913-551-7963 |
| OPP                     | Anna Lowit,                 | 703-308-4135 |
|                         | Karen Hamernik, and         | CANNOT FIND  |
|                         | Susan Laessig               | 202-564-5232 |
| OW                      | Greg Miller                 | 202-566-2310 |
| Region 5                | Kimberely Harris            | 312-886-4239 |
| OUTM                    |                             | 702 602 0704 |
| OLEM                    | Marlene Berg                | 703-603-8701 |
| Region 2                | Marian Olsen                | 212-637-4313 |
| Region 9                | Patrick Wilson              | 415-972-3354 |
| DOD                     |                             |              |
| OAR                     | Bob Hetes and               | 919-541-1589 |
|                         | Deirdre Murphy              | 919-541-0729 |
| OW                      | Greg Miller                 | 202-566-2310 |
| Region 10               | Marc Stifelman              | 206-553-6979 |



| OAR's number 3 priority on 2014        |
|----------------------------------------|
| Orac statistics of profits of 2014     |
| regional interests are superfund based |
|                                        |
|                                        |
|                                        |
|                                        |
|                                        |
| OM/less where 2 and of the an 2014     |
| OW's number 2 priority on 2014         |
|                                        |
|                                        |
|                                        |
|                                        |
| OA's number 12 priority on 2014        |
| OW's number 12 priority on 2014        |
|                                        |
|                                        |
|                                        |
|                                        |



#### Message

**Sent**: 2/8/2018 6:05:02 PM

To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Champlin, Anna [Champlin.Anna@epa.gov]; Avery, James

[Avery.James@epa.gov]

**CC**: Lehman, Rachel [lehman.rachel@epa.gov]

Subject: RE: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

Yeah, but

Ex. 5 - Deliberative Process

From: Bahadori, Tina

Sent: Thursday, February 8, 2018 1:01 PM

To: Champlin, Anna <Champlin.Anna@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Avery, James

<Avery.James@epa.gov>

Cc: Lehman, Rachel < lehman.rachel@epa.gov>

Subject: RE: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

#### Ex. 5 - Deliberative Process

From: Champlin, Anna

Sent: Thursday, February 8, 2018 12:47 PM

To: Bahadori, Tina < Bahadori. Tina@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>; Avery, James

<<u>Avery.James@epa.gov</u>>

Cc: Lehman, Rachel < lehman.rachel@epa.gov>

Subject: RE: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

Tina –

#### Ex. 5 - Deliberative Process

Anna (Osaka) Champlin

National Center for Environmental Assessment

EPA Office of Research and Development

(Desk) 202-564-8074 (Cell) Ex. 6 - Personal Privacy

From: Bahadori, Tina

Sent: Wednesday, February 07, 2018 6:16 PM

To: Champlin, Anna <Champlin.Anna@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Avery, James

<<u>Avery.James@epa.gov</u>>

Cc: Lehman, Rachel < lehman.rachel@epa.gov>

Subject: RE: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

I think this is very good Anna. I made some minor edits below highlighted in yellow.

Tina

From: Champlin, Anna

Sent: Wednesday, February 7, 2018 4:02 PM

To: Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Avery, James

<<u>Avery.James@epa.gov</u>>



Cc: Lehman, Rachel < lehman.rachel@epa.gov>

Subject: FW: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

Hi Tina,

Below is a draft response to a media inquiry that we received this week about the formaldehyde assessment. The reporter's questions are below and concern this article

(https://www.sciencedirect.com/science/article/pii/S027323001730363X) published last week. The reporter would like a response by this Friday.

#### **REPORTER QUESTIONS:**

- Do we have any comment we would like to make about the review?
- Do we accept the conclusions of the review?
- Are we planning to re-issue the IRIS?

#### **DRAFT REPONSE:**

## Ex. 5 - Deliberative Process

Thanks,

Anna (Osaka) Champlin
National Center for Environmental Assessment
EPA Office of Research and Development
(Desk) 202-564-8074
(Cell) Ex. 6 - Personal Privacy

From: Sauerhage, Maggie

Sent: Tuesday, February 6, 2018 9:14:54 AM

To: Lehman, Rachel; Champlin, Anna

Cc: Hubbard, Carolyn; Maguire, Megan; D'Amico, Louis

Subject: Media Chem. Risk Manager - Formaldehyde/Leukaemia - 2/9

Hi ladies – please see below for an inquiry from Chemical Risk Manager. They're wondering if we'd like to comment on a recently published review in Regulatory Toxicology and Pharmacology which disputes a link between formaldehyde and leukemia as suggested by the 2010 draft IRIS assessment. The deadline is the end of this week.

#### The questions are:

- Do we any comment we would like to make about the review?
- Do we accept the conclusions of the review?
- Are we planning to re-issue the IRIS? (not entirely clear on this one)



OUTLET CHEMICAL RISK MANAGER
REPORTER JUDITH CHAMBERLAIN
DDL FRIDAY 2/9

Good morning colleagues, Can we help this reporter?

++

I work for a chemical news agency called Chemical Risk Manager, which is part of Chemical Watch and we were interested to read a review in Regulatory Toxicology and Pharmacology which disputes a link between formaldehyde and leukaemia as suggested by the 2010 draft IRIS assessment.

I wonder if you have any comment you would like to make about the review and if you accept the conclusions and also whether you are planning to re-issue the IRIS?

The review was published in a peer-reviewed journal (Regulatory Toxicology and Pharmacology) last week I think and this is the link:

https://www.sciencedirect.com/science/article/pii/S027323001730363X

If you could get a comment on this for me that would be great. Ideally I would need a response by the end of the week if possible.

Many thanks Judith



From: Soto, Vicki [Soto.Vicki@epa.gov]

**Sent**: 1/18/2018 12:45:48 PM

To: Thayer, Kris [thayer.kris@epa.gov]
Subject: RE: IRIS Management Council - BC

## Ex. 5 - Deliberative Process

This is the latest I have,

Ex. 5 - Deliberative Process

From: Thayer, Kris

Sent: Thursday, January 18, 2018 7:42 AM
To: Soto, Vicki <Soto.Vicki@epa.gov>
Subject: RE: IRIS Management Council - BC

#### Ex. 5 - Deliberative Process

From: Soto, Vicki

**Sent:** Thursday, January 18, 2018 7:32 AM **To:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a> **Subject:** RE: IRIS Management Council - BC

#### Ex. 5 - Deliberative Process



## Ex. 5 - Deliberative Process

From: Thayer, Kris

Sent: Thursday, January 18, 2018 6:44 AM
To: Soto, Vicki < Soto, Vicki@epa.gov >
Subject: RE: IRIS Management Council - BC

I am hosting a guest today, am I critical for this? Or can I join for a portion of the time?

----Original Appointment-----

From: Soto, Vicki

Sent: Tuesday, January 16, 2018 9:17 AM

To: Soto, Vicki; Woodall, George; Lee, Janice; Avery, James; Subramaniam, Ravi; Rieth, Susan; Morozov, Viktor; Saint,

Chris; Garcia, Kelly; Persad, Amanda; Thayer, Kris

Subject: IRIS Management Council - BC

When: Thursday, January 18, 2018 1:30 PM-2:30 PM (UTC-05:00) Eastern Time (US & Canada).

Where:

Hi everyone,

Please save this time for an IRIS Management Council BC meeting this week. Agenda to follow.

#### Ex. 6 - Personal Privacy

RTP: B-230. RRB: 51104



#### Message

From: Thayer, Kris [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3CE4AE3F107749C6815F243260DF98C3-THAYER, KRI]

**Sent**: 10/11/2017 1:12:25 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]
CC: Glenn, Barbara [Glenn.Barbara@epa.gov]

**Subject**: Re: Next Steps on Formaldehyde - updated schedule

#### Ex. 5 - Deliberative Process

Sent from my iPhone

On Oct 11, 2017, at 8:16 AM, Kraft, Andrew < Kraft. Andrew@epa.gov > wrote:

#### Ex. 5 - Deliberative Process

From: Thayer, Kris

Sent: Wednesday, October 11, 2017 8:08 AM
To: Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft, Andrew@epa.gov</a>
Cc: Glenn, Barbara < Glenn, Barbara@epa.gov>

Subject: Re: Next Steps on Formaldehyde - updated schedule

Sorry to be remedial but remind me what the conclusion was in 2011 and NAS opinion of the conclusion?

Sent from my iPhone

On Oct 11, 2017, at 7:49 AM, Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov</a>> wrote:

#### Ex. 5 - Deliberative Process

From: Thayer, Kris

Sent: Wednesday, October 11, 2017 7:12 AM

To: Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >

Subject: RE: Next Steps on Formaldehyde - updated schedule

#### Ex. 5 - Deliberative Process



#### Ex. 5 - Deliberative Process

None of this is new, but with Bob's retirement imminent we may have to rely more on Bruce to help us get this out the door...

<image001.png>

From: Bahadori, Tina

Sent: Friday, October 6, 2017 2:40 PM

To: Soto, Vicki <Soto. Vicki@epa.gov>; Kraft, Andrew <Kraft. Andrew@epa.gov>; Glenn,

Barbara < Glenn.Barbara@epa.gov >

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico, Louis@epa.gov</u>>; Ross, Mary <<u>Ross, Mary@epa.gov</u>>; Bussard, David

<Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris

<thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

Exactly – when the schedule has so many moving and fluid parts, it becomes even more imperative to track the placeholders. Let's not become discouraged. Ex. 5 - Deliberative Process

#### Ex. 5 - Deliberative Process

Thanks again for being so very great – all of you.

Tina

From: Soto, Vicki

Sent: Thursday, October 5, 2017 8:20 AM



**To:** Kraft, Andrew < Kraft.Andrew@epa.gov >; Glenn, Barbara < Glenn.Barbara@epa.gov >; Bahadori, Tina < Bahadori, Tina@epa.gov >

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Shams, Dahnish < Shams. Dahnish@epa.gov>; Jones, Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>; Ross, Mary < Ross. Mary@epa.gov>; Bussard, David < Bussard. David@epa.gov>; Lavoie, Emma < Lavoie. Emma@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

Just throwing in my 2 more cents. I realize that the schedule is fluid and the further out you go, the more wishy-washy it gets, the program still needs some sort of place holder for some of these milestones.

From: Kraft, Andrew

Sent: Thursday, October 05, 2017 8:13 AM

To: Soto, Vicki <Soto.Vicki@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>;

Bahadori, Tina < Bahadori, Tina@epa.gov >

Cc: Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico, Louis@epa.gov</u>>; Ross, Mary <<u>Ross, Mary@epa.gov</u>>; Bussard, David <<u>Bussard, David@epa.gov</u>>; Lavoie, Emma <<u>Lavoie, Emma@epa.gov</u>>; Thayer, Kris <thayer, kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

With the steps that are obviously being added (per Tina's email), this schedule will surely change. However, I'm not sure the schedule itself is really worth the effort at this point. I, personally, would rather focus on addressing the "fluid" deliverables and not worry about this (sorry).

Tina, per your question about the overview, I believe Barbara and I could prioritize revising that for Bob so that he could have it before the end of October (note: the underlying assumption we are working with is that Barbara and I are exclusively focusing on formaldehyde this month). As for the other asks, I suppose we can take them in stride as they become more "firm" in terms of date and scope.

Patiently,

Andrew and (speaking for) Barbara

From: Soto, Vicki

Sent: Wednesday, October 04, 2017 8:03 PM

**To:** Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Cc: Ramasamy, Santhini <Ramasamy, Santhini@epa.gov>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico,

Louis <DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Bussard, David

<<u>Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Thayer, Kris</u>

<thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

Hi everyone,



#### Ex. 5 - Deliberative Process

Vicki

## Ex. 5 - Deliberative Process



## Ex. 5 - Deliberative Process



From: Glenn, Barbara

Sent: Thursday, September 28, 2017 11:24 AM

**To:** Bahadori, Tina <a href="mailto:Bahadori.Tina@epa.gov">Bahadori.Tina@epa.gov">Bussard, David <a href="mailto:Bussard.David@epa.gov">Bussard, David <a href="mailto:Bussard.David@epa.gov">Bussard, David@epa.gov</a>; Thayer, Kris <a href="mailto:Kris@epa.gov">thayer, Kris@epa.gov</a>; Lavoie,

Emma < Lavoie. Emma@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary

< Ross. Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hi Tina

#### Ex. 5 - Deliberative Process

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 11:10 AM

**To:** Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft, Andrew@epa.gov</a>; Glenn, Barbara < <a href="mailto:Glenn.Barbara@epa.gov">Glenn, Barbara < a href="mailto:Glenn.Barbara@epa.gov">Glenn, Glenn.Barbara@epa.gov</a href="mailto:Glenn.Barbara@epa.gov">Glenn, Gle

Emma <Lavoie.Emma@epa.gov>

Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

Thanks Andrew. So, with this timeline, can we punctuate the rest of the timeline?

#### Ex. 5 - Deliberative Process

Tina

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 10:35 AM

**To:** Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>; Glenn, Barbara

<<u>Glenn.Barbara@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Thayer, Kris

<thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>



Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki < Soto.Vicki@epa.gov>; Shams, Dahnish < Shams.Dahnish@epa.gov>; Jones, Samantha < Jones, Samantha@epa.gov>; D'Amico, Louis < DAmico, Louis@epa.gov>; Ross, Mary < Ross, Mary@epa.gov>

**Subject:** RE: Next Steps on Formaldehyde

Hi Tina,

#### Ex. 5 - Deliberative Process

-Barbara and Andrew

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:05 PM

**To:** Glenn, Barbara < Glenn.Barbara@epa.gov>; Kraft, Andrew < Kraft.Andrew@epa.gov>; Bussard, David < Bussard.David@epa.gov>; Thayer, Kris < thayer.kris@epa.gov>; Lavoie,

Emma <<u>Lavoie.Emma@epa.gov</u>>

Cc: Ramasamy, Santhini <Ramasamy, Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

**Subject:** RE: Next Steps on Formaldehyde

#### Ex. 5 - Deliberative Process

From: Glenn, Barbara

Sent: Tuesday, September 26, 2017 9:03 AM

**To:** Bahadori, Tina <a href="mailto:Rahadori.Tina@epa.gov">Raft, Andrew <a href="mailto:Kraft.Andrew@epa.gov">Kraft, Andrew@epa.gov</a>; Bussard, David <a href="mailto:Bussard.David@epa.gov">Bussard, David@epa.gov</a>; Thayer, Kris <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov</a>; Lavoie,

Emma <<u>Lavoie.Emma@epa.gov</u>>



Cc: Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

Subject: RE: Next Steps on Formaldehyde

بمنات مللمالا

#### Ex. 5 - Deliberative Process

Thanks, Andrew and Barbara

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 8:27 AM

**To:** Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Bussard, David < Bussard. David@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Lavoie, Emma < Lavoie. Emma@epa.gov >

Cc: Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Soto, Vicki

<<u>Soto.Vicki@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <Ross.Mary@epa.gov>

Subject: FW: Next Steps on Formaldehyde

Hi Everyone,

#### Ex. 5 - Deliberative Process

Other thoughts?

T.

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) < yamada.richard@epa.gov>

Cc: Kavlock, Robert < Kavlock, Robert@epa.gov>; Rodan, Bruce < rodan.bruce@epa.gov>;

Orme-Zavaleta, Jennifer <<u>Orme-Zavaleta Jennifer@epa.gov</u>>; Gwinn, Maureen <<u>gwinn.maureen@epa.gov</u>>; Sjogren, Mya <<u>Sjogren.Mya@epa.gov</u>>; Kuhn, Kevin



<Kuhn.Kevin@epa.gov>; Fegley, Robert <Fegley.Robert@epa.gov>; Ross, Mary
<Ross.Mary@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis
<<u>DAmico.Louis@epa.gov</u>>; Thayer, Kris <thayer.kris@epa.gov>; Bussard, David
<Bussard.David@epa.gov>

Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday — I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices — Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

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Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile: [Ex.6-Personal Privacy Email: Bahadori, Tina@epa.gov



#### Message

From: Thayer, Kris [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3CE4AE3F107749C6815F243260DF98C3-THAYER, KRI]

**Sent**: 11/1/2017 7:46:13 PM

To: Sjogren, Mya [Sjogren.Mya@epa.gov]

CC: Fleming, Megan [Fleming.Megan@epa.gov]

Subject: RE: Formaldehyde Science Discussion

Mya,

We weren't planning on providing materials – the discussion points are pretty familiar to Bruce. Thanks!

From: Sjogren, Mya

Sent: Wednesday, November 1, 2017 11:29 AM

To: Thayer, Kris <thayer.kris@epa.gov>

**Cc:** Fleming, Megan <Fleming.Megan@epa.gov> **Subject:** RE: Formaldehyde Science Discussion

Hi Kris,

Should we expect materials for this meeting? If so, when might they be available?

Thanks.

Mya Sjogren Immediate Office of the Assistant Administrator Office of Research and Development US EPA (202) 564-2213

----Original Appointment----

From: Rodan, Bruce

Sent: Wednesday, October 25, 2017 8:55 AM

To: Rodan, Bruce; Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming,

Megan

**Subject:** Formaldehyde Science Discussion

When: Thursday, November 02, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41226 RRB/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

- Barbara Glenn
- Andrew Kraft
- Tom Bateson
- Kris Thayer

At first glance Tuesday 10/31/17 at noon looks good @ on everyone's calendar. Hopefully we can snag that soon!!

Thanks,

Tina



#### Message

From: Thayer, Kris [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3CE4AE3F107749C6815F243260DF98C3-THAYER, KRI]

**Sent**: 9/25/2017 1:53:50 PM

To: Boone, Amanda [Boone.Amanda@epa.gov]

CC: Fritz, Jason [Fritz.Jason@epa.gov]; Rieth, Susan [Rieth.Susan@epa.gov]; Avery, James [Avery.James@epa.gov];

Shams, Dahnish [Shams.Dahnish@epa.gov]; Lee, Janice [Lee.JaniceS@epa.gov]; Subramaniam, Ravi

[Subramaniam.Ravi@epa.gov]; McNeil, Simone [mcneil.simone@epa.gov]; Soto, Vicki [Soto.Vicki@epa.gov]; Persad,

Amanda [Persad.Amanda@epa.gov]

**Subject**: RE: IO Weekly Report for 09/25/17

#### Ex. 5 - Deliberative Process

From: Fritz, Jason

Sent: Monday, September 25, 2017 9:32 AM

To: Boone, Amanda <Boone.Amanda@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Rieth, Susan <Rieth.Susan@epa.gov>; Avery, James <Avery.James@epa.gov>; Shams, Dahnish <Shams.Dahnish@epa.gov>; Lee, Janice <Lee.JaniceS@epa.gov>; Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; McNeil, Simone <mcneil.simone@epa.gov>; Soto, Vicki <Soto.Vicki@epa.gov>; Persad, Amanda <Persad.Amanda@epa.gov> Subject: RE: IO Weekly Report for 09/25/17

Hello,

Here's an update from me – I presenting a seminar for the same class that Michele apparently did a few weeks ago.

## Ex. 5 - Deliberative Process

Thanks!

jf

From: Boone, Amanda

Sent: Monday, September 25, 2017 8:27 AM

**To:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov">thayer.kris@epa.gov</a>; Rieth, Susan < <a href="mailto:Rieth.Susan@epa.gov">thayer.kris@epa.gov</a>; Avery, James < <a href="mailto:Avery.James@epa.gov">Avery, James < <a href="mailto:Avery.James@epa.gov">Avery, James < <a href="mailto:Avery.James@epa.gov">Avery, James < <a href="mailto:Avery.James@epa.gov">hones</a>; Subramaniam.Ravi@epa.gov</a>; McNeil, Simone < <a href="mailto:mone@epa.gov">mone@epa.gov</a>; Soto, Vicki < <a href="mailto:Soto.Vicki@epa.gov">Soto.Vicki@epa.gov</a>; Persad,

Amanda < Persad. Amanda@epa.gov >; Fritz, Jason < Fritz. Jason@epa.gov >

Subject: RE: IO Weekly Report for 09/25/17

Importance: High

Hi Kris!



I'll incorporate your additions. No, I don't get the reports from the other divisions....but I will now.

All,

Are there any other additions or changes? The cut-off time is Noon today.

Thanks, Amanda B.

From: Thayer, Kris

Sent: Monday, September 25, 2017 8:21 AM

**To:** Rieth, Susan <a href="mailto:Rieth.Susan@epa.gov">Rieth.Susan@epa.gov">Rieth.Susan@epa.gov</a>; Boone, Amanda <a href="mailto:Boone.Amanda@epa.gov">Roone.Amanda@epa.gov</a>; Avery, James <a href="mailto:Amanda@epa.gov">Avery, James<a href="mailto:Amanda@epa.gov">Roone.Amanda@epa.gov</a>; Lee, Janice <a href="mailto:Lee.JaniceS@epa.gov">Lee.JaniceS@epa.gov</a>; Subramaniam, Ravi <a href="mailto:Subramaniam.Ravi@epa.gov">Soto, Vicki</a>; Soto.Vicki@epa.gov</a>; Persad, Amanda <a href="mailto:Persad.Amanda@epa.gov">Persad.Amanda@epa.gov</a>; Fritz, Jason <a href="mailto:Fritz.Jason@epa.gov">Fritz.Jason@epa.gov</a>>

**Subject:** RE: IO Weekly Report for 09/25/17

My additions below. Busy month!

Amanda – do you get the weekly reports from other NCEA Divisions? If so, can we start circulating them routinely to IRIS Division when they are sent to Tina and Lou? – anything to help communication and awareness....

From: Rieth, Susan

Sent: Friday, September 22, 2017 4:36 PM

**To:** Boone, Amanda <<u>Boone.Amanda@epa.gov</u>>; Avery, James <<u>Avery.James@epa.gov</u>>; Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Lee, Janice <<u>Lee.JaniceS@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Subramaniam, Ravi <<u>Subramaniam.Ravi@epa.gov</u>>; McNeil, Simone <<u>mcneil.simone@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>;

Persad, Amanda < Persad. Amanda@epa.gov>; Fritz, Jason < Fritz. Jason@epa.gov>

**Subject:** Re: IO Weekly Report for 09/25/17

Hi Amanda,

I can't think of anything new to add, but suggest that you can drop the ones with strikeout below.

thanks,

Sue

From: Boone, Amanda

Sent: Friday, September 22, 2017 12:09 PM

To: Avery, James; Shams, Dahnish; Lee, Janice; Rieth, Susan; Thayer, Kris; Subramaniam, Ravi; McNeil, Simone; Soto,

Vicki; Persad, Amanda; Fritz, Jason Subject: IO Weekly Report for 09/25/17

Good afternoon!



Below is the text of as well as the Sharepoint link to the Draft IO Weekly Report for 9/25/17. Please sbmit any additions or changes to me by Noon on Monday, September 25. **Sharepoint Link:** https://usepa.sharepoint.com/sites/ORD\_Work/IMC/IRIS\_Division/\_layouts/15/guestaccess.aspx?guestaccesstoken=tAT nLOU1pvBRH56JUaaEkDd%2f4HZJW%2b1OK7yShzOPg7c%3d&docid=2\_18bf2eb47b3144c558758aee4a6686613&rev=1 Text: **MAJOR ANNOUNCEMENTS:** Ex. 5 - Deliberative Process Availability of the Integrated Risk Information System ...

www.federalregister.gov

The Environmental Protection Agency (EPA) is announcing a 30- day



public comment period associated with the draft IRIS Assessment Plans for Nitrate/Nitrite

**NOTABLES:** 

# Ex. 5 - Deliberative Process

STAFF RECOGNITION/PUBLICATIONS:

30-DAY OUTLOOK FOR PRESENTATIONS AND EXTERNAL MEETINGS:

# Ex. 5 - Deliberative Process





\*\* Reported Previously

Thanks,

Amanda B.

From: Boone, Amanda

Sent: Monday, September 18, 2017 7:58 AM

**To:** Shams, Dahnish <<u>Shams.Dahnish@epa.gov</u>>; Lee, Janice <<u>Lee.JaniceS@epa.gov</u>>; Rieth, Susan

<<u>Rieth.Susan@epa.gov</u>>; Thayer, Kris <<u>thayer.kris@epa.gov</u>>; Subramaniam, Ravi <<u>Subramaniam.Ravi@epa.gov</u>>; Avery, James <<u>Avery.James@epa.gov</u>>; McNeil, Simone <<u>mcneil.simone@epa.gov</u>>; Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Persad,

Amanda < Persad. Amanda@epa.gov>; Fritz, Jason < Fritz. Jason@epa.gov>

Subject: IO Weekly Report for 09/18/17

Importance: High

Good morning!

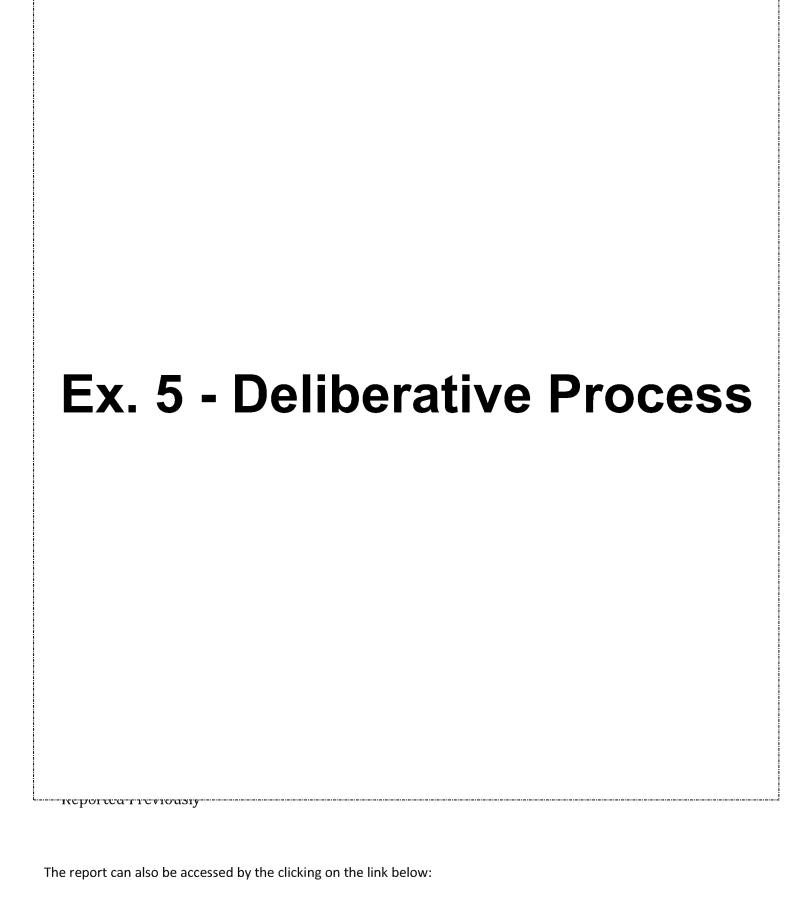
Please review the edited Weekly IO Report for this week (9/18/17) on the <u>IRIS Division SharePoint</u> site via the link provided below (the report text is also provided below in the body of this email) and <u>reply</u> with any edits that need to be addressed or to confirm that no changes are needed. **Please respond by Noon on Monday, September 18.** 



The report can also be accessed by the clicking on the link

below: https://usepa.sharepoint.com/sites/ORD\_Work/IMC/IRIS\_Division/\_layouts/15/DocIdRedir.aspx?ID=SSYEHYHTR\_5TA-1665725469-118





Amanda W. Boone



National Center for Environmental Assessment

Office of Research & Development

U.S. Environmental Protection Agency

One Potomac Yard (South Building), Suite S11611 | 2777 S. Crystal Drive | Arlington, VA 22202

Office: 703-347-8654



Thayer, Kris [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP From:

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=3CE4AE3F107749C6815F243260DF98C3-THAYER, KRI]

Sent: 9/22/2017 9:01:43 PM

Lowit, Anna [Lowit.Anna@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov] To:

Subject:

From: White, Kimberly [mailto:Kimberly\_White@americanchemistry.com]

Sent: Wednesday, September 20, 2017 11:01 AM

Cc: Swenberg, James A <jswenber@email.unc.edu>; mundt@email.unc.edu; Hartwell, Hadley J

<hadley\_hartwell@med.unc.edu>

Subject: Re: Formaldehyde Science Invited Expert Workshop

Dear Formaldehyde Science Invited Expert Workshop Participants;

Thank you for your interest in participating in the Invited Expert Workshop to explore the latest science on formaldehyde carcinogenicity being held October 10 -11, 2017 at the UNC Friday Center located at 100 Friday Center Drive, Chapel Hill, NC 27599. The Workshop will be co-chaired by Dr. Jim Swenberg and Dr. Ken Mundt and the Workshop discussion will focus on ((1) review the evidence of causal relationships between formaldehyde exposure and cancer; (2) discuss the role of integrating available scientific data to reach conclusions regarding carcinogenicity; (3) identify data requirements and gaps regarding cancer hazard and risk assessment, and (4) identify key endpoints, data, and preferred formats for developing objective and transparent risk assessments. The authors of many relevant studies of formaldehyde and cancer risk have been invited to participate in this Workshop as well as senior scientists with expertise in hazard assessment, mode of action analysis, integration of evidence and quantitative risk assessment.

In preparation for the Workshop, please review the following additional relevant information:

1. Workshop Materials - A link has been provided here

https://acc.ftpstream.com/38419/091e9d5010d144889dd9e4a5ee4cebd5/Formaldehyde%2bWorkshop%2bMaterials.zip where you can download all the meeting materials, which include:

- Tentative Workshop Agenda
- Participants List
- Charge Questions
- Suggested Reading List

The Workshop agenda includes a considerable allotment of time for participant discussion on the charge questions. Every attendee is encouraged to review the charge questions and actively provide input during the workshop discussion. In the charge questions document, a proposed list of participants has been identified related to each charge question based on area of expertise but all participants should feel free to provide input on any charge question. While not required, if participants wish to prepare 1-2 slides to highlight a topic are presented in the charge questions feel free to do so.

- Travel Reimbursements For those receiving travel reimbursements, please be sure to return all completed forms to Ms. Hadley Hartwell at the University of North Carolina (email: hadley\_hartwell@med.unc.edu) as soon as possible. If you have questions regarding any of the required forms please contact Ms. Hartwell directly.
- October 10th Dinner For those available, the workshop organizers will host a participants dinner at 6:30pm. If you are planning to attend please RSVP to Kimberly White (email: Kimberly\_White@amerianchemistry.com) by September 30th.

We look forward to your participation in the workshop and please do hesitate to contact me, Ms. Hartwell or the workshop chairs with any questions.

Kind Regards,

Kimberly Wise White, Ph.D. | American Chemistry Council Senior Director, Chemical Products & Technology Division Kimberly\_White@americanchemistry.com 700 2nd Street NE | Washington, DC | 20002 o: (202) 249-6707 C: (202) 341-7602 www.americanchemistry.com

the individual named. If you are not the named addressee do not disseminate, distribute or copy this email. Please notify the sender immediately by email if you have received this email by mistake and delete this email from your system. E-mail transmission cannot be guaranteed to be secure or error-free as information could be intercepted, corrupted, lost, destroyed, arrive late or incomplete, or contain viruses. The sender therefore does not accept liability for any errors or omissions in the contents of



this message which arise as a result of email transmission. American Chemistry Council, 700 - 2nd Street NE, Washington, DC 20002, www.americanchemistry.com ----Original Message----From: Lowit, Anna Sent: Friday, September 22, 2017 4:57 PM To: Lavoie, Emma <Lavoie.Emma@epa.gov> Cc: Thayer, Kris <thayer.kris@epa.gov> Subject: Re: ? I just heard about it too and am trying to find the agenda. Is there a website? Can't find it just trying to google. Sent from my iPhone > On Sep 22, 2017, at 4:55 PM, Lavoie, Emma <Lavoie.Emma@epa.gov> wrote: > Yes....Mundt apparently co-organized - is in UNC Oct 10. Copying Kris Thayer here who is going. Iris Camacho just told me about it today and she is planning to attend also. > Do staff need to get together before the meeting? > -Emma > > Emma T. Lavoie, PhD > Tel: 703-347-0328 > ----Original Message----> From: Lowit, Anna > Sent: Friday, September 22, 2017 4:40 PM > To: Lavoie, Emma <Lavoie.Emma@epa.gov> > Subject: ? > Hey Emma > Do you know anything about an upcoming workshop on formaldehyde, maybe on cancer? > Anna



> Sent from my iPhone

To: Feeley, Drew (Robert)[feeley.robert@epa.gov]

From: Yamada, Richard (Yujiro)
Sent: Fri 9/22/2017 5:46:55 PM
Subject: FW: Formaldehyde - TIMELY

From: Beck, Nancy

Sent: Thursday, September 7, 2017 9:50 PM

**To:** Dravis, Samantha <a href="mailto:samantha@epa.gov">dravis.samantha@epa.gov</a>

Cc: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>

Subject: Re: Formaldehyde - TIMELY

Samantha,

Richard and I were talking about this assessment yesterday.

Ex. 5 - Deliberative Process

## Ex. 5 - Deliberative Process

Nancy.

Nancy B. Beck, Ph.D., DABT Deputy Assistant Administrator, OCSPP

P: <u>202-564-1273</u> M: <u>202-731-9910</u> Beck.Nancy@epa.gov

On Sep 7, 2017, at 9:39 PM, Dravis, Samantha < dravis.samantha@epa.gov > wrote:

Nancy: Can you look into this?

Sent from my iPhone

Begin forwarded message:

From: "Newberry, Edward" < edward.newberry@squirepb.com>

**Date:** September 7, 2017 at 5:18:16 PM EDT



**To:** "dravis.samantha@epa.gov" <dravis.samantha@epa.gov> **Subject:** Formaldehyde - TIMELY

Hi Sam,

I just received an urgent call from one of our clients, who manufactures, among other things, formaldehyde. They have been told that Tina Bahadori, Director of NCEA at EPA, (she a career employee who assumed the director job this past January), has told people that she will release – as soon as next week – a toxicological assessment for formaldehyde. That assessment is expected to claim, based on a single small and flawed (flawed according to the National Academy of Sciences) study of Chinese workers that has been contradicted by other credible research, a link between formaldehyde and leukemia. According to the industry, the negative impacts of releasing such a study, particularly one that is contradicted by the weight of scientific evidence, are broad and enormous and this is the highest issue for the company. Other big companies like Georgia Pacific and others would be affected as well.

Senior management would like to meet with the Administrator as soon as possible – critical because they are told release of the report may come next week. Is that something that can be arranged? I am calling the Scott's office (I left a message for Millan) as well but wanted to give you a head's up and see if you could help. I am told that Ryan has been briefed on this and another colleague of mine is reaching out to him.

Hope you are well. I also wanted to follow up on the Potash Corporation issue we discussed a couple of weeks ago (summary below). Client (PCS) is eager to meet with you and the others as we discussed. Any chance we can get something set up for next week?

Thanks Sam.

Ed

Begin forwarded message:

From: "Newberry, Edward" <edward.newberry@squirepb.com>

Date: August 25, 2017 at 5:04:13 PM EDT

To: "dravis.samantha@epa.gov" <dravis.samantha@epa.gov>
Cc: "Winters, Karen A." <karen.winters@squirepb.com>,

"Jessica.DeMonte@potashcorp.com" < Jessica.DeMonte@potashcorp.com>

Subject: PotashCorp

Sam.



Thanks for talking with me earlier this week. We represent PotashCorp, the largest fertilizer company in the world producing potash, nitrogen and phosphate. Its subsidiary PCS Phosphate, has two phosphate mines in the US, one of which is located in Aurora, North Carolina.

As we discussed, we'd like to come in and visit with you, Brittany and Mandy Gunasakara about a rule implemented during the Obama-era. See *Phosphoric Manufacturing and Phosphate Fertilizer Production RTR and Standards of Performance for Phosphate Processing, 80 Fed. Reg. 50386 (August 19, 2015)*. The rule establishes mercury emissions limits for existing calciners (a calciner is a rotating steel cylinder used to heat and process the phosphate rock). The Aurora calciners are the only calciners in the country subject to the limit. The mercury limit is based on a statistically limited data set not representative of existing conditions. The limit also fails to take into account the variability of the mercury in the phosphate rock, which PCS Phosphate has no ability to control.

In setting the limit, US EPA determined that there was no adverse health risk associated with mercury emissions from the Aurora facility. EPA's Research Triangle Park office has expressed interest in working with PCS Phosphate to revise the limits, but has indicated they need direction from EPA headquarters.

The issue is critical because the projected cost of emissions controls may impact the viability of the facility, along with the jobs of its 850 employees and the hundreds of collateral businesses and jobs that support the facility and its operations. Moreover, controls are untested and may in fact prove not to be feasible.

North Carolina has already provided PCS Phosphate with what relief they can, however a new limit must be set and addressed through a rule revision on the federal level.

I would appreciate it if you were able to meet with me and my partner, Karen



Winters, along with Jessica DeMonte, senior counsel for PCS. We are flexible on scheduling however anytime next Wednesday or Thursday or the week of September 11 would be best.

Thanks again. I look forward to seeing you.

| Ed                         |  |
|----------------------------|--|
|                            |  |
| 46 Offices in 21 Countries |  |

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| #US |      |      |
|-----|------|------|
|     | <br> | <br> |



From: Woodall, George [Woodall.George@epa.gov]

**Sent**: 1/5/2018 1:48:26 PM

To: Bussard, David [Bussard.David@epa.gov]

Subject: RE: HCHO

Agreed. Context is critical.

How is the work in the RAF going? Do you feel more at home since you first came on?

George

From: Bussard, David

**Sent:** Friday, January 05, 2018 8:35 AM

To: Woodall, George < Woodall. George@epa.gov>

**Subject:** RE: HCHO

I got it. Many thanks! The context is useful.

From: Woodall, George

**Sent:** Thursday, January 04, 2018 3:34 PM **To:** Bussard, David < <u>Bussard.David@epa.gov</u>>

Subject: RE: HCHO

He just responded with additional details. I will forward...

From: Bussard, David

Sent: Thursday, January 04, 2018 3:33 PM

To: Woodall, George < Woodall.George@epa.gov >

Subject: FW: HCHO

George,

Thanks for including Barbara and Andrew. Can you also include me in any emails re formaldehyde?

#### Ex. 5 - Deliberative Process

David

From: Woodall, George

Sent: Thursday, January 4, 2018 1:25 PM

To: Bradfield, John

Cc: Lavoie, Emma; Vasu, Amy; Rimer, Kelly; Glenn, Barbara; Kraft, Andrew

Subject: RE: HCHO

John,

# Ex. 5 - Deliberative Process

At present, the IRIS assessment for formaldehyde remains in development. You can look at the IRIS web site for an update

(https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance nmbr=419&forceAssessmentTab=t rue). I have also copied the Assessment Managers – Barbara Glenn and Andrew Kraft – on this message in case they have more to offer or you would like to contact them directly with specific questions (no need for me to play middle man); however, feel free to cc: me on any correspondence.

Formaldehyde CASRN 50-00-0 | IRIS | US EPA, ORD

cfpub.epa.gov

This IRIS assessment for Formaldehyde consists of hazard identification and dose-response assessment data and provides support for EPA risk management decisions.

I hope this helps Ex. 6 - Personal Privacy

George

\*\*\*\*\*\*\*

George M. Woodall, PhD
Toxicologist
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

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Location: B231-D, EPA-RTP Main Campus

Office: (919) 541-3896 Mobile: (919) 280-8165

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Postal Address: US EPA, MD B243-01, Research Triangle Park, NC 27711

Package Delivery: US EPA, MD B243-01, 4930 Old Page Road, Durham, NC 27703 Physical Address: US EPA, 109 TW Alexander Drive, Research Triangle Park, NC 27709

\*\*\*\*\*

From: Bradfield, John

**Sent:** Wednesday, January 03, 2018 3:17 PM **To:** Woodall, George < <u>Woodall.George@epa.gov</u>>

Subject: HCHO



|                                                                                                                             | George - As we head into     | the next heat on the PCWP RTR marathon, Industry is asking us about h | าealth |  |  |
|-----------------------------------------------------------------------------------------------------------------------------|------------------------------|-----------------------------------------------------------------------|--------|--|--|
|                                                                                                                             | benchmarks.                  | Ex. 5 - Deliberative Process                                          |        |  |  |
| į                                                                                                                           | Ex. 5 - Deliberative Process |                                                                       |        |  |  |
| Ex. 5 - Dailbeard true Process: S that accurate? If so, so you know who the ORD Principle Investigator on formal dehyde is? |                              |                                                                       |        |  |  |
|                                                                                                                             | Thanks.                      |                                                                       |        |  |  |

John Bradfield Environmental Engineer

U.S. EPA I Natural Resources Group I Sector Policies and Programs Division, OAQPS 109 T.W. Alexander Drive (Mail Drop E143-03) I Research Triangle Park, NC 27711 Phone: 919.541.3062 I email: <a href="mailto:Bradfield.John@epa.gov">Bradfield.John@epa.gov</a>



From: Bussard, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CF26B876393E44F38BDD06DB02DBBFE5-BUSSARD, DAVID]

**Sent**: 10/12/2017 7:32:29 PM

To: Lavoie, Emma [Lavoie.Emma@epa.gov]

Subject: RE: TSCA and externally-done risk assessments

I'm trying to figure out how this might work if industry requests an assessment of some formaldehyde uses and provides a draft assessment. Does that mean Nancy then ignores the IRIS effort and OCSPP does their own assessment building on the draft assessment from a manufacturer?

I don't think there is any legal reason IRIS could not still move forward, but it could be part of an Administration decision that an IRIS assessment independent of the submitted draft "is not needed".

From: Lavoie, Emma

Sent: Thursday, October 12, 2017 2:05 PM

To: Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>

Subject: RE: TSCA and externally-done risk assessments

I'll note that if an outside evaluation is submitted, OPPT hardly has the resources to actually review it.....so if the only timeline identified is the 3 years timeline in the section 6 risk eval section, then maybe they have 3 years to review it?!

-Emma

.....

Emma T. Lavoie, PhD Tel: 703-347-0328

From: Bussard, David

Sent: Thursday, October 12, 2017 12:16 PM

To: Lavoie, Emma < Lavoie. Emma@epa.gov >; Ramasamy, Santhini < Ramasamy. Santhini@epa.gov >

Subject: TSCA and externally-done risk assessments

#### **STATUTE**

The only statutory mention of externally-done risk assessments I can find is in Section 26 (I)(5):

(5) GUIDANCE.—Not later than 1 year after the date of enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, the Administrator shall develop guidance to assist interested persons in developing and submitting draft risk evaluations which shall be considered by the Administrator. The guidance shall, at a minimum, address the quality of the information submitted and the process to be followed in developing draft risk evaluations for consideration by the Administrator. [p. 74 of the statutory text Gino sent.]

#### **GUIDANCE and RULE TEXT**

The guidance says that in order for a draft assessment to be used in whole or in part by EPA, it will be most useful if it meets the requirements EPA assessments need to meet. It does not need to be peer reviewed – in that if EPA uses it in its draft assessment it will then undergo peer review as EPA presents its draft.



#### RE FORMALDEHYDE,

I also note that the TSCA rule on risk assessments does not legally apply to risk assessments initiated in support of other statutes or programs.

David A. Bussard

Director, Washington Division National Center for Environmental Assessment (NCEA) Office of Research and Development, USEPA



From: Bussard, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CF26B876393E44F38BDD06DB02DBBFE5-BUSSARD, DAVID]

**Sent**: 10/11/2017 7:02:06 PM

To: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]

Subject: FW: FA

Can you find and think about how this would work?

I recall the amended TSCA may have procedures for an external party to file a risk assessment, but I have not studied them or thought about how those might relate to our doing our IRIS review.

David

From: Jones, Samantha

Sent: Wednesday, October 11, 2017 10:43 AM

**To:** Thayer, Kris <thayer.kris@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Ross, Mary <Ross.Mary@epa.gov> **Subject:** RE: FA

ounjeun ne. . . .

On formaldehyde? ....now?

From: Thayer, Kris

Sent: Wednesday, October 11, 2017 10:40 AM

To: Bussard, David <<u>Bussard.David@epa.gov</u>>; Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>> Subject: FA

My sense from the ACC meeting is they are aiming toward a 3rd party SR submission

Sent from my iPhone



From: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]

**Sent**: 9/7/2017 9:38:38 PM

**To**: Kraft, Andrew [Kraft.Andrew@epa.gov]

CC: Bussard, David [Bussard.David@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]

Subject: Re: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of Formaldehyde

(Inhalation)

My understanding is that Tina's office is responding.

Sent from my iPhone

On 7 Sep 2017, at 14:49, Kraft, Andrew < <u>Kraft.Andrew@epa.gov</u> > wrote:

Any movement on this? We should probably craft a response sooner rather than later...

From: Bussard, David

Sent: Thursday, August 31, 2017 8:30 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>; Jones, Samantha

<Jones.Samantha@epa.gov>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>; Hagerthey, Scot <<u>Hagerthey.Scot@epa.gov</u>>; Thayer, Kris <thayer.kris@epa.gov>

**Subject:** Fwd: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of Formaldehyde (Inhalation)

## Ex. 5 - Deliberative Process

One attempt to craft a response is in email below.

**David Bussard** 

Begin forwarded message:

From: "Jones, Samantha" < <u>Jones Samantha@epa.gov</u>>

**Date:** August 30, 2017 at 11:48:38 PM EDT

To: "Bussard, David" < Bussard David@epa.gov >, "Birchfield, Norman"

< Birchfield.Norman@epa.gov >, "Ramasamy, Santhini"

<Ramasamy.Santhini@epa.gov>, "D'Amico, Louis" <DAmico.Louis@epa.gov>,

"Glenn, Barbara" < Glenn Barbara@epa.gov >, "Hagerthey, Scot"

<Hagerthey.Scot@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS Toxicological Review of Formaldehyde (Inhalation)

## Ex. 5 - Deliberative Process



It would be good to broach the subject with Tina before responding.

Samantha

From: Bussard, David

Sent: Wednesday, August 30, 2017 10:28 AM

**To:** Jones, Samantha < <u>Jones.Samantha@epa.gov</u>>; Birchfield, Norman

<Birchfield.Norman@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>;

Hagerthey, Scot < Hagerthey. Scot@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values from IRIS

Toxicological Review of Formaldehyde (Inhalation)

### Ex. 5 - Deliberative Process

From: Jones, Samantha

Sent: Wednesday, August 30, 2017 10:14 AM

To: Bussard, David < Bussard. David@epa.gov >; Birchfield, Norman

<Birchfield.Norman@epa.gov>; Ramasamy, Santhini

<<u>Ramasamy.Santhini@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>;

Glenn, Barbara < Glenn.Barbara@epa.gov >; Hagerthey, Scot

<Hagerthey.Scot@epa.gov>

Subject: RE: Request by RIVM for permission to use the approach and values

from IRIS Toxicological Review of Formaldehyde (Inhalation)

There is an opportunity here. Do we have any idea about their timeframe??

Samantha Jones, PhD
NCEA Associate Director for Health (acting)
HHRA Interim Deputy National Program Director
USEPA, ORD/NCEA
703-347-8580

From: Bussard, David

Sent: Wednesday, August 30, 2017 10:10 AM

To: Birchfield, Norman < Birchfield.Norman@epa.gov >; Ramasamy, Santhini

<<u>Ramasamy.Santhini@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>;

Glenn, Barbara < Glenn.Barbara@epa.gov >; Hagerthey, Scot

< Hagerthey. Scot@epa.gov >; Jones, Samantha < Jones. Samantha@epa.gov >

**Subject:** FW: Request by RIVM for permission to use the approach and values

from IRIS Toxicological Review of Formaldehyde (Inhalation)

This is likely "a Tina issue", but let's see if we can generate a recommendation or some options.

Is this a possible response?



David

From: Kraft, Andrew

Sent: Wednesday, August 30, 2017 8:04 AM

To: Birchfield, Norman < Birchfield.Norman@epa.gov >; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>

Cc: Bussard, David <Bussard.David@epa.gov>; D'Amico, Louis

<<u>DAmico.Louis@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>

Subject: Fw: Request for permission to use data from IRIS Toxicological Review

of Formaldehyde (Inhalation)

I'm guessing we will need a fairly quick and succinct response. Please forward as appropriate.

-Andrew

From: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl>

**Sent:** Tuesday, August 29, 2017 7:59 AM

To: Kraft, Andrew

Cc: Els Smit; Paul Janssen; Joke Herremans

Subject: Request for permission to use data from IRIS Toxicological Review of

Formaldehyde (Inhalation)

Dear Dr Kraft,



My name is Lidka Maslankiewicz and I work at the Dutch National Institute for Public Health and the Environment (RIVM). We are currently busy with the update of the Maximum Permissible Risk (MPR) for formaldehyde.

We would like to use the approach and values described in IRIS Toxicological Review of Formaldehyde (Inhalation) (External Review Draft 2010), in particular Volume 3: "Quantitative Assessment, Major Conclusions in the Characterization of Hazard and Dose Response" (<a href="https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614">https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614</a>), to derive MPR value for the Netherlands. Could you, please, inform me, if this could be permitted? Are there more recent versions of this document? If we would be allowed to use your data, how we could refer to the source?

IRIS Toxicological Review of Formaldehyde (Inhalation ...

#### cfpub.epa.gov

EPA announces the release of the Toxicological Review of Formaldehyde-Inhalation Assessment in the June 2 Federal Register Notice. This draft assessment is ...

Kind regards

Lidka

Lidka Maslankiewicz
National Institute for Public Health and the Environment (RIVM)
Centre for Safety of Substances and Products
tel. 31 (0)30 2743160
+31 6 46 86 07 73
fax. 31 (0)30 2744401

e-mail: Lidka.Maslankiewicz@rivm.nl

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te melden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

www.rivm.nl De zorg voor morgen begint vandaag

<image001.jpg>

RIVM

www.rivm.nl

Dit Nederlandse overheidsinstitut



verzorgt informa monitoring en wetenschappelijk onderbouwing v volksgezondheid Ook valt het informatiecentru

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<image002.jpg>

Rijksinstituur voor Volksgezon en Milieu - I

#### www.rivm.nl

Substances of ve concern hamper recycling. Substavery high concern (SVHC) can hamp safe recycling of streams in the Netherlands.

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te melden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

www.rivm.nl De zorg voor morgen begint vandaag



<image001.jpg>

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#### www.rivm.nl

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<image002.jpg>

Rijksinstituur voor Volksgezon en Milieu - I

#### www.rivm.nl

Substances of ve concern hamper recycling. Substa very high concern (SVHC) can hamp safe recycling of streams in the Netherlands.



From: Radke-Farabaugh, Elizabeth [radke-farabaugh.elizabeth@epa.gov]

**Sent**: 10/23/2017 1:45:45 PM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]

Subject: RE: Question about formaldehyde assessment

#### Thanks!

From: Glenn, Barbara

Sent: Monday, October 23, 2017 9:41 AM

To: riesd@michigan.gov

**Cc:** Kraft, Andrew < Kraft. Andrew@epa.gov>; Bussard, David < Bussard. David@epa.gov>; Ramasamy, Santhini < Ramasamy. Santhini@epa.gov>; Soto, Vicki < Soto. Vicki@epa.gov>; Rieth, Susan < Rieth. Susan@epa.gov>; Radke-Farabaugh, Elizabeth < radke-farabaugh.elizabeth@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>; Subramaniam,

Ravi <Subramaniam.Ravi@epa.gov>

Subject: Question about formaldehyde assessment

Dear Dr. Ries,

As team leaders for the formaldehyde assessment, we are responding to your letter dated 10/06/17 to the IRIS Hotline. We apologize for the delayed response to your inquiry about the formaldehyde assessment. Our revision of the formaldehyde assessment is almost complete and will be ready to begin our review process soon. The review process is comprehensive; it involves review by other offices within EPA, review by other federal agencies, a public comment period, as well as an independent peer review that, for this assessment, will be conducted by the National Academies of Sciences. Given the timelines necessary to complete these steps, we do not expect that the final assessment will be posted during 2018.

You also asked about whether we will be changing conclusions about the mutagenic mode-of-action for the IUR. At this point, we regret that we are not able to discuss the specifics of the conclusions in the document.

Sincerely,

Barbara Glenn and Andrew Kraft



From: Bussard, David [Bussard.David@epa.gov]

**Sent**: 10/8/2017 6:20:46 PM

To: Kraft, Andrew [Kraft.Andrew@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Glenn, Barbara

[Glenn.Barbara@epa.gov]

**Subject**: RE: Next Steps on Formaldehyde - updated schedule

Rereading this, maybe we don't need to meet.

Sounds like you are comfortable with focus on completing document this month.

Some side efforts to put together a list of potential 'vulnerabilities' or help Samantha to do that.

Let me know if we need to talk.

David

From: Kraft, Andrew

**Sent:** Friday, October 06, 2017 3:42 PM

To: Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Glenn,

Barbara < Glenn. Barbara@epa.gov>

Subject: Re: Next Steps on Formaldehyde - updated schedule

# Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Note that Barbara is on leave

until Wednesday of next week.

# Ex. 5 - Deliberative Process

-Andrew

From: Bussard, David

Sent: Friday, October 6, 2017 3:22 PM

**To:** Ramasamy, Santhini; Kraft, Andrew; Glenn, Barbara **Subject:** FW: Next Steps on Formaldehyde - updated schedule

### Ex. 5 - Deliberative Process

David



From: Bahadori, Tina

**Sent:** Friday, October 06, 2017 2:40 PM

To: Soto, Vicki <Soto.Vicki@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara

<Glenn.Barbara@epa.gov>

**Cc:** Ramasamy, Santhini < <a href="mailto:Ramasamy.Santhini@epa.gov">Ramasamy, Santhini < <a href="mailto:Shams.Dahnish@epa.gov">Shams, Dahnish < <a href="mailto:Shams.Dahnish@epa.gov">Shams.Dahnish@epa.gov</a>>; Jones,

Samantha < <u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis < <u>DAmico.Louis@epa.gov</u>>; Ross, Mary

<Ross.Mary@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>;

Thayer, Kris < thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

# Ex. 5 - Deliberative Process

Thanks again for being so very great – all of you.

Tina

From: Soto, Vicki

Sent: Thursday, October 5, 2017 8:20 AM

**To:** Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Bahadori, Tina < Bahadori. Tina@epa.gov >

Cc: Ramasamy, Santhini < Ramasamy.Santhini@epa.gov>; Shams, Dahnish < Shams.Dahnish@epa.gov>; Jones,

Samantha < <u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis < <u>DAmico.Louis@epa.gov</u>>; Ross, Mary

<Ross.Mary@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>;

Thayer, Kris <thayer.kris@epa.gov>

**Subject:** RE: Next Steps on Formaldehyde - updated schedule

Just throwing in my 2 more cents. I realize that the schedule is fluid and the further out you go, the more wishywashy it gets, the program still needs some sort of place holder for some of these milestones.

From: Kraft, Andrew

Sent: Thursday, October 05, 2017 8:13 AM

**To:** Soto, Vicki <<u>Soto.Vicki@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Bahadori, Tina <<u>Bahadori.Tina@epa.gov</u>>

 $\textbf{Cc:} \ Ramasamy, Santhini < \underline{Ramasamy.Santhini@epa.gov}; \ Shams, \ Dahnish < \underline{Shams.Dahnish@epa.gov}; \ Jones, \ Lamasamy, \ Santhini < \underline{Ramasamy.Santhini@epa.gov}; \ Lamasamy, \$ 

Samantha < Jones. Samantha@epa.gov>; D'Amico, Louis < DAmico. Louis@epa.gov>; Ross, Mary

<<u>Ross.Mary@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>;



Patiently,

Andrew and (speaking for) Barbara

From: Soto, Vicki

Sent: Wednesday, October 04, 2017 8:03 PM

**To:** Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Bahadori, Tina <<u>Bahadori, Tina@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>

**Cc:** Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>; Shams, Dahnish <<u>Shams, Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones, Samantha@epa.gov</u>>; D'Amico, Louis <<u>DAmico, Louis@epa.gov</u>>; Ross, Mary

<Ross.Mary@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>;

Thayer, Kris <thayer.kris@epa.gov>

Subject: RE: Next Steps on Formaldehyde - updated schedule

#### Hi everyone,

I tried to take the bullets below and wrap them into the schedule of Formaldehyde in Project. I've thrown in some highlighting to pull attention to some of those dates. I think it seems really tight. The lines that are 0 duration are milestones (for reports-most of them are a brown color) and can be ignored. This can always be altered if it doesn't make sense.

Vicki

# Ex. 5 - Deliberative Process





From: Glenn, Barbara

Sent: Thursday, September 28, 2017 11:24 AM

To: Bahadori, Tina <a href="mailto:Kraft">Bahadori.Tina@epa.gov</a>; Kraft, Andrew <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov</a>; Bussard, David@epa.gov</a>; Bussard, David@epa.gov</a>; Cavoie, Emma <a href="mailto:Lavoie.Emma@epa.gov">Lavoie, Emma <a href="mailto:Lavoie.Emma@epa.gov">Lavoie.Emma@epa.gov</a>> Ca: Ramasamy, Santhini@epa.gov</a>; Soto, Vicki <a href="mailto:Soto.Vicki@epa.gov">Soto.Vicki@epa.gov</a>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hi Tina,

# Ex. 5 - Deliberative Process

From: Bahadori, Tina

Sent: Thursday, September 28, 2017 11:10 AM

To: Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; Bussard, David < Bussard. David@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Lavoie, Emma < Lavoie. Emma@epa.gov > Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov >; Soto, Vicki < Soto, Vicki@epa.gov >; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Thanks Andrew. So, with this timeline, can we punctuate the rest of the timeline?



Tina

From: Kraft, Andrew

Sent: Thursday, September 28, 2017 10:35 AM

To: Bahadori, Tina <Bahadori, Tina@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov> Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki < Soto, Vicki@epa.gov>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hi Tina,

# Ex. 5 - Deliberative Process

-Barbara and Andrew

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 12:05 PM

To: Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov> Cc: Ramasamy, Santhini < Ramasamy, Santhini@epa.gov>; Soto, Vicki < Soto, Vicki@epa.gov>; Shams, Dahnish

<Shams.Dahnish@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Thanks Barbara This is a good timeline Ex. 5 - Deliberative Process



T.

From: Glenn, Barbara

Sent: Tuesday, September 26, 2017 9:03 AM

**To:** Bahadori, Tina <a href="mailto:Kraft">Bahadori</a>. Tina@epa.gov</a>; Kraft, Andrew <a href="mailto:Kraft">Kraft</a>. Andrew@epa.gov</a>; Bussard, David@epa.gov</a>; Bussard, David@epa.gov</a>; Cavoie, Emma <a href="mailto:Lavoie.Emma@epa.gov">Lavoie.Emma@epa.gov</a>>
<a href="mailto:Cc: Ramasamy">Cc: Ramasamy</a>, Santhini <a href="mailto:Ramasamy">Ramasamy</a>, Santhini@epa.gov</a>; Soto, Vicki <a href="mailto:Soto.Vicki@epa.gov">Soto.Vicki@epa.gov</a>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>

Subject: RE: Next Steps on Formaldehyde

Hello Tina.

# Ex. 5 - Deliberative Process

Thanks, Andrew and Barbara

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 8:27 AM

**To:** Kraft, Andrew < <a href="mailto:Kraft.Andrew@epa.gov">Kraft.Andrew@epa.gov</a>; Glenn, Barbara < <a href="mailto:Glenn.Barbara@epa.gov">Glenn.Barbara@epa.gov</a>; Bussard, David@epa.gov</a>; Bussard, David@epa.gov</a>; Lavoie, Emma < <a href="mailto:Lavoie.Emma@epa.gov">Lavoie.Emma@epa.gov</a></a> **Cc:** Ramasamy, Santhini <a href="mailto:Ramasamy.Santhini@epa.gov">Ramasamy.Santhini@epa.gov</a>; Soto, Vicki <a href="mailto:Soto.Vicki@epa.gov">Soto.Vicki@epa.gov</a>; Shams, Dahnish

<<u>Shams.Dahnish@epa.gov</u>>; Jones, Samantha <<u>Jones.Samantha@epa.gov</u>>; D'Amico, Louis

<<u>DAmico.Louis@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>

Subject: FW: Next Steps on Formaldehyde

Hi Everyone,

# Ex. 5 - Deliberative Process

Other thoughts?

T.

From: Bahadori, Tina

Sent: Tuesday, September 26, 2017 7:21 AM

To: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>



Cc: Kavlock, Robert < Kavlock, Robert@epa.gov >; Rodan, Bruce < rodan.bruce@epa.gov >; Orme-Zavaleta, Jennifer < Orme-Zavaleta\_Jennifer@epa.gov >; Gwinn, Maureen < gwinn.maureen@epa.gov >; Sjogren, Mya < Sjogren, Mya@epa.gov >; Kuhn, Kevin < Kuhn, Kevin@epa.gov >; Fegley, Robert < Fegley, Robert@epa.gov >; Ross, Mary < Ross, Mary@epa.gov >; Jones, Samantha < Jones, Samantha@epa.gov >; D'Amico, Louis < DAmico, Louis@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Bussard, David < Bussard.David@epa.gov > Subject: Next Steps on Formaldehyde

Good Morning Richard,

I wanted to let you know that the IOAA formaldehyde briefing went well yesterday — I am sorry you were not able to participate. We are going to take the feedback from Bob and Bruce and reflect them in the draft of the assessment that is being prepared for Agency (within EPA) review. We expect our documents to be ready for transmittal to EPA IRIS review partners within a month. In the meantime, we will schedule briefings for the various offices — Office of Air is particularly anxious for this briefing.

Please let me know if you need additional information.

Tina

Tina Bahadori, Sc.D.

Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

PYS phone: 703-347-0283; RTP phone: 919-541-0855 Mobile: [Ex.6-Personal Privacy]; Email: <u>Bahadori, Tina@epa.gov</u>



From: Bussard, David [Bussard.David@epa.gov]

**Sent**: 1/5/2018 1:20:26 PM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]

Subject: RE: HCHO

A preview of ACC arguments...

Thx

From: Glenn, Barbara

**Sent:** Friday, January 05, 2018 7:13 AM **To:** Bussard, David <Bussard.David@epa.gov> **Cc:** Kraft, Andrew <Kraft.Andrew@epa.gov>

Subject: FW: HCHO

FYI

From: Bradfield, John

Sent: Thursday, January 04, 2018 3:19 PM

To: Woodall, George < Woodall. George @epa.gov >

Cc: Lavoie, Emma <Lavoie, Emma@epa.gov>; Vasu, Amy <Vasu, Amy@epa.gov>; Rimer, Kelly

<<u>Rimer.Kelly@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>;

Dunkins, Robin < Dunkins. Robin@epa.gov>; Hanks, Katie < hanks.katie@epa.gov>; Spence, Kelley

<Spence.Kelley@epa.gov>; Hirtz, James < Hirtz.James@epa.gov>

Subject: RE: HCHO

# Ex. 5 - Deliberative Process

It looks like our old friend formaldehyde is back, if it ever left.

John Bradfield

**Environmental Engineer** 

U.S. EPA I Natural Resources Group I Sector Policies and Programs Division, OAQPS 109 T.W. Alexander Drive (Mail Drop E143-03) I Research Triangle Park, NC 27711

Phone: 919.541.3062 | email: Bradfield.John@epa.gov

From: Woodall, George

**Sent:** Thursday, January 04, 2018 1:26 PM **To:** Bradfield, John < <u>Bradfield, John@epa.gov</u>>

Cc: Lavoie, Emma <<u>Lavoie.Emma@epa.gov</u>>; Vasu, Amy <<u>Vasu.Amy@epa.gov</u>>; Rimer, Kelly

<Rimer.Kelly@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>

Subject: RE: HCHO

John,



At present, the IRIS assessment for formaldehyde remains in development. You can look at the IRIS web site for an update

(https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance\_nmbr=419&forceAssessmentTab=true). I have also copied the Assessment Managers – Barbara Glenn and Andrew Kraft – on this message in case they have more to offer or you would like to contact them directly with specific questions (no need for me to play middle man); however, feel free to cc: me on any correspondence.

I hope this helps. Ex. 6 - Personal Privacy

George \*\*\*\*\*\*\*\*

George M. Woodall, PhD

Toxicologist

National Center for Environmental Assessment

Office of Research and Development

U.S. Environmental Protection Agency

Location: B231-D, EPA-RTP Main Campus

Office: (919) 541-3896 Mobile: Ex. 6 - Personal Privacy

Postal Address: US EPA, MD B243-01, Research Triangle Park, NC 27711

Package Delivery: US EPA, MD B243-01, 4930 Old Page Road, Durham, NC 27703 Physical Address: US EPA, 109 TW Alexander Drive, Research Triangle Park, NC 27709

\*\*\*\*\*\*

From: Bradfield, John

Sent: Wednesday, January 03, 2018 3:17 PM
To: Woodall, George < Woodall. George @epa.gov>

Subject: HCHO

George - As we head into the next heat on the PCWP RTR marathon, Industry is asking us about health

benchmarks. Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Er. 5-Deliberative Process If so, do you know who the ORD Principle Investigator on formaldehyde is? Thanks.

John Bradfield

**Environmental Engineer** 

U.S. EPA I Natural Resources Group I Sector Policies and Programs Division, OAQPS 109 T.W. Alexander Drive (Mail Drop E143-03) I Research Triangle Park, NC 27711

Phone: 919.541.3062 | email: Bradfield.John@epa.gov



From: Ito, Satoru [Ito.Satoru@epa.gov]

**Sent**: 10/26/2017 3:56:19 PM

To: Glenn, Barbara [Glenn.Barbara@epa.gov]

**Subject**: Add Reference Request for Formaldehyde [TEAMHERO-113552]

Hi Barbara,

Your add reference request has been processed. The following references were tagged to the **Human Cancer Studies >> Screened >> Epi** tags under the IRIS **Formaldehyde** project.

#### Saberi et al., 2013

Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC)

https://hero.epa.gov/heronet/index.cfm/reference/details/reference\_id/2969929

>>> Supplement

https://hero.epa.gov/heronet/index.cfm/reference/details/reference\_id/4113448

#### Talibov et al., 2014

Occupational exposure to solvents and acute myeloid leukemia: a population-based, case-control study in four Nordic countries

https://hero.epa.gov/heronet/index.cfm/reference/details/reference\_id/2799600

Please let me know if you have questions or concerns regarding these references.

Best,

-Sato

Satoru Ito
HERO Senior Data Specialist
National Center for Environmental Assessment
ORISE Grantee
US Environmental Protection Agency
Research Triangle Park, NC 27711
919-541-1343



From: Glenn, Barbara [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7A2DC9210D2D4D02A623B33F87F49436-GLENN, BARBARA]

**Sent**: 10/23/2017 1:34:17 PM

To: Radke-Farabaugh, Elizabeth [radke-farabaugh.elizabeth@epa.gov]; Rieth, Susan [Rieth.Susan@epa.gov]; Kraft,

Andrew [Kraft.Andrew@epa.gov]; Bussard, David [Bussard.David@epa.gov]

CC: Pratt, Margaret [pratt.margaret@epa.gov]; Rutigliano, Marian [Rutigliano.Marian@epa.gov]; Soto, Vicki

[Soto.Vicki@epa.gov]; D'Amico, Louis [DAmico.Louis@epa.gov]

Subject: RE: Form submission from: IRIS Contact us about the Integrated Risk Information System form

Thanks Beth. We worked out a response and I'll be sending it today. -Barbara ----Original Message----From: Radke-Farabaugh, Elizabeth Sent: Monday, October 23, 2017 9:32 AM To: Rieth, Susan <Rieth.Susan@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov> Cc: Pratt, Margaret <pratt.margaret@epa.gov>; Rutigliano, Marian <Rutigliano.Marian@epa.gov>; Soto, Vicki <Soto.Vicki@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov> Subject: RE: Form submission from: IRIS Contact us about the Integrated Risk Information System form Hi all, any update on this? ----Original Message----From: Rieth, Susan Sent: Friday, October 6, 2017 11:38 AM To: Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Bussard, David <Bussard.David@epa.gov> Cc: Radke-Farabaugh, Elizabeth <radke-farabaugh.elizabeth@epa.gov>; Pratt, Margaret Andrew, Barbara and David, I'm forwarding the following query to the IRIS Hotline from the state of Michigan regarding formaldehyde. Lou also received this email. Not sure how you want to respond to the question on the formaldehyde IUR or release of the assessment. Let us know and we can get back to the Hotline with an appropriate response. Thanks. Sue ----Original Message----From: King, Bernard Sent: Friday, October 06, 2017 11:22 AM To: Radke-Farabaugh, Elizabeth <radke-farabaugh.elizabeth@epa.gov>; Rieth, Susan <Rieth.Susan@epa.gov>; Rutigliano, Marian <Rutigliano.Marian@epa.gov>; Pratt, Margaret <pratt.margaret@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>; Soto, Vicki <Soto.Vicki@epa.gov> Cc: Semeniuk, Michael <Semeniuk.Michael@epa.gov> Subject: FW: Form submission from: IRIS Contact us about the Integrated Risk Information System form FYI Thank you for contacting the IRIS Hotline. Sincerely, Bernard King IRIS Hotline EPA Docket Center Records Information Manager III Artic Slope Mission Services (ASMS) - Contractor Phone: (202) 566-1676 Email: king.bernard@epa.gov



From: drupal\_admin [mailto:drupal\_admin@epa.gov]

Sent: Friday, October 06, 2017 11:10 AM To: IRIS HOTLINE <IRIS\_HOTLINE@epa.gov>

Subject: Form submission from: IRIS Contact us about the Integrated Risk Information System form

Submitted on 10/06/2017 11:09AM Submitted values are:

Name: Dr Divinia Ries Email: riesd@michigan.gov

Comments: We are updating the Michigan cleanup criteria for formaldehyde and initially proposed the use of 2010 IRIS draft's IURF value and the recommendation for mutagenic MOA classification. Due to stakeholder comment, we are now proposing the IRIS 1991 IURF value but retained the MMOA application. Question - Is it likely the final revised or final assessment will be out in 2018? Are you likely changing the MMOA mechanism? Thanks!

Web Area: IRIS



#### Message

From: Glenn, Barbara [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7A2DC9210D2D4D02A623B33F87F49436-GLENN, BARBARA]

**Sent**: 10/19/2017 6:42:35 PM

To: D'Amico, Louis [DAmico.Louis@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Kraft, Andrew

[Kraft.Andrew@epa.gov]

CC: Subramaniam, Ravi [Subramaniam.Ravi@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]

**Subject**: RE: response to IRIS Hotline letter

Thanks Lou ( I'll send this response by COB today.

From: D'Amico, Louis

Sent: Thursday, October 19, 2017 2:30 PM

To: Bussard, David <Bussard.David@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara

<Glenn.Barbara@epa.gov>

Cc: Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>

Subject: RE: response to IRIS Hotline letter

Some suggested edits:

Dear Dr. Ries,

### Ex. 5 - Deliberative Process

Sincerely,

Barbara Glenn and Andrew Kraft

Louis D'Amico, Ph.D.

Assistant Center Director for Communications and Regulatory Support (Acting)

U.S. EPA, ORD/NCEA

damico.louis@epa.gov

O: (703) 347-0344 M Ex. 6 - Personal Privacy

From: Bussard, David

Sent: Wednesday, October 18, 2017 12:19 PM

To: Kraft, Andrew < Kraft. Andrew@epa.gov >; Glenn, Barbara < Glenn. Barbara@epa.gov >; D'Amico, Louis

<DAmico.Louis@epa.gov>



Cc: Subramaniam, Ravi <<u>Subramaniam.Ravi@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>> **Subject:** RE: response to IRIS Hotline letter

Once I reread, as written is okay.

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Lou, is it okay as is?

Alternative could be, to avoid someone else misreading it:

### Ex. 5 - Deliberative Process

From: Kraft, Andrew

Sent: Wednesday, October 18, 2017 11:14 AM

To: Bussard, David < Bussard.David@epa.gov >; Glenn, Barbara < Glenn.Barbara@epa.gov >; D'Amico, Louis

<DAmico.Louis@epa.gov>

Cc: Subramaniam, Ravi <Subramaniam.Ravi@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>

**Subject:** RE: response to IRIS Hotline letter

I am fine with either version. Thanks!

From: Bussard, David

Sent: Wednesday, October 18, 2017 11:05 AM

To: Glenn, Barbara <Glenn.Barbara@epa.gov>; D'Amico, Louis <DAmico.Louis@epa.gov>

Cc: Subramaniam, Ravi <<u>Subramaniam.Ravi@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Ramasamy,

Santhini <<u>Ramasamy.Santhini@epa.gov</u>> **Subject:** RE: response to IRIS Hotline letter

We might need Tina's eye on the description, but I'm okay with first paragraph.

## Ex. 5 - Deliberative Process

David

From: Glenn, Barbara

**Sent:** Wednesday, October 18, 2017 10:58 AM **To:** D'Amico, Louis < <u>DAmico, Louis@epa.gov</u>>

**Cc:** Subramaniam, Ravi <<u>Subramaniam.Ravi@epa.gov</u>>; Kraft, Andrew <<u>Kraft.Andrew@epa.gov</u>>; Bussard, David <<u>Bussard.David@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy, Santhini@epa.gov</u>>

Subject: response to IRIS Hotline letter

How's this for an answer?

### Ex. 5 - Deliberative Process



### Ex. 5 - Deliberative Process

Sincerely, Barbara Glenn and Andrew Kraft

From: drupal\_admin [mailto:drupal\_admin@epa.gov]

Sent: Friday, October 06, 2017 11:10 AM

To: IRIS HOTLINE < IRIS HOTLINE@epa.gov>

Subject: Form submission from: IRIS Contact us about the Integrated Risk Information System

form

Submitted on 10/06/2017 11:09AM Submitted values are:

Name: Dr Divinia Ries Email: riesd@michigan.gov

Comments: We are updating the Michigan cleanup criteria for formaldehyde and initially proposed the use of 2010 IRIS draft's IURF value and the recommendation for mutagenic MOA classification. Due to stakeholder comment, we are now proposing the IRIS 1991 IURF value but retained the MMOA application. Question - Is it likely the final revised or final assessment will be out in 2018? Are you likely changing the MMOA mechanism? Thanks!

Web Area: IRIS



#### Message

From: Glenn, Barbara [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7A2DC9210D2D4D02A623B33F87F49436-GLENN, BARBARA]

**Sent**: 9/22/2017 4:06:01 PM

**To**: Kraft, Andrew [Kraft.Andrew@epa.gov]

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

I be calling in from my home

From: Kraft, Andrew

**Sent:** Friday, September 22, 2017 11:43 AM **To:** Glenn, Barbara <Glenn.Barbara@epa.gov>

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

remote from home, or from Tina's office? If you are going to be remote from Tina's office, I will probably just join you there (from previous conversations, it sounded like Tina wanted it to be remote-only). Happy Friday!

From: Glenn, Barbara

Sent: Friday, September 22, 2017 11:30 AM

To: Bahadori, Tina; Kraft, Andrew; Thayer, Kris; Lavoie, Emma; Ramasamy, Santhini; Jones, Samantha; Ross, Mary;

Hagerthey, Scot

Cc: Bussard, David; D'Amico, Louis

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

I will need to join remotely. Thanks.

From: Bahadori, Tina

Sent: Friday, September 22, 2017 11:23 AM

**To:** Kraft, Andrew < Kraft.Andrew@epa.gov >; Thayer, Kris < thayer.kris@epa.gov >; Lavoie, Emma < Lavoie.Emma@epa.gov >; Ramasamy, Santhini < Ramasamy.Santhini@epa.gov >; Jones, Samantha

Cc: Bussard, David <<u>Bussard.David@epa.gov</u>>; Glenn, Barbara <<u>Glenn.Barbara@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

That's Ok, the point was we can find a path forward with RIVM after we see the signals on Monday.

On Monday, we were going to go in person to RRB for the briefing, although I have reserved my conference room with video connection, if you or anyone would prefer to do it remotely. I think either way is fine.



From: Kraft, Andrew

Sent: Friday, September 22, 2017 11:15 AM

**To:** Thayer, Kris < thayer.kris@epa.gov>; Bahadori, Tina < Bahadori, Tina@epa.gov>; Lavoie, Emma

<<u>Lavoie.Emma@epa.gov</u>>; Ramasamy, Santhini <<u>Ramasamy.Santhini@epa.gov</u>>; Jones, Samantha

<<u>Jones.Samantha@epa.gov</u>>; Ross, Mary <<u>Ross.Mary@epa.gov</u>>; Hagerthey, Scot <<u>Hagerthey.Scot@epa.gov</u>>

**Cc:** Bussard, David < <u>Bussard.David@epa.gov</u>>; Glenn, Barbara < <u>Glenn.Barbara@epa.gov</u>>; D'Amico, Louis

<DAmico.Louis@epa.gov>

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Chatting on Monday might be tough-I have meetings stacked until 4, and Barbara is leaving to teach a class around 3. Maybe it's a break time during SAB (after our ppts)-type talk?

Also, we are all just planning on attending the briefing remotely on Monday, correct (i.e. no one is going over in person)?

From: Thayer, Kris

Sent: Friday, September 22, 2017 7:44 AM

To: Kraft, Andrew; Bahadori, Tina; Lavoie, Emma; Ramasamy, Santhini; Jones, Samantha; Ross, Mary; Hagerthey, Scot

Cc: Bussard, David; Glenn, Barbara; D'Amico, Louis

Subject: RE: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Let's discuss how best to respond after Monday briefing....

From: Kraft, Andrew

Sent: Friday, September 22, 2017 7:43 AM

To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Ramasamy, Santhini

<Ramasamy.Santhini@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Ross, Mary <Ross.Mary@epa.gov>;

Hagerthey, Scot < Hagerthey. Scot@epa.gov>

Cc: Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Glenn, Barbara

<<u>Glenn.Barbara@epa.gov</u>>; D'Amico, Louis <<u>DAmico.Louis@epa.gov</u>>

Subject: Fw: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Just forwarding this to the wider group that was asked to weigh in on the prior email. Please see below.



From: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl>

Sent: Friday, September 22, 2017 4:54 AM

To: Kraft, Andrew

Cc: Bussard, David; D'Amico, Louis; Els Smit; Glenn, Barbara; Joke Herremans; Paul Janssen; Thayer, Kris; Theo Vermeire

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Andrew and Barbara

Thank you for your reply, apologies for not answering sooner.

The issue is that we would like to use the data as presented in the 2010 Draft, more specifically the quantification of cancer risks for NPC (Nasopharyngeal Cancer), based either on human data and on animal data.

From your mail, we understand that the information is not to be cited as the EPA position. That was not our intention, but rather we want to include the unit risks as a scientific approach that has been developed and that we need to take on board.

Could it be possible to use the information, if we explicitly include a disclaimer? Something in line with: "It should be noted that the methodology used for the quantification of cancer risk for NPC (Nasopharyngeal Cancer), has not been formalised and should not be seen as the official position of the EPA. From a scientific viewpoint, however, we consider this approach as valid and use unit risk to derive the Maximum Permissible Risk (MPR)."

We also noted that in 2014 US-EPA convened a workshop (<a href="https://www.epa.gov/sites/production/files/2014-12/documents/formaldehyde\_workshop\_agenda\_final.pdf">https://www.epa.gov/sites/production/files/2014-12/documents/formaldehyde\_workshop\_agenda\_final.pdf</a>), the topics of which were the endogenous formation of formaldehyde and its relation to formaldehyde toxicity and the mechanistic evidence for lymphohematopoietic cancer induction by formaldehyde. Any further information on these topics and on the envisaged timeline for finalization of the US-EPA IRIS evaluation would be very welcome.

April 30th to May 1st, 2014 Crystal City Marriott at ...

www.epa.gov

Luoping Zhang, University of California at Berkeley, discussant Robert Snyder, Rutgers University (retired), discussant Martha Sandy, California EPA, discussant

Maybe we can first do the exchange via mail and decide later on if a telephone conference is useful.

Kind regards

Lidka

Lidka Maslankiewicz National Institute for Public Health and the Environment (RIVM) Centre for Safety of Substances and Products tel. 31 (0)30 2743160



+31 6 46 86 07 73 fax. 31 (0)30 2744401

e-mail: Lidka.Maslankiewicz@rivm.nl

From: "Kraft, Andrew" < Kraft. Andrew@epa.gov >

To: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl >,

Co: Els Smit <<u>els.smit@rivm.nl</u>>, Paul Janssen <<u>paul.janssen@rivm.nl</u>>, "Joke Herremans" <<u>joke.herremans@rivm.nl</u>>, "Glenn, Barbara"

<Glenn Barbara@epa.gov>, "D'Amico, Louis" <DAmico.Louis@epa.gov>, "Bussard, David" <Bussard David@epa.gov>, "Thayer, Kris" <thayer.kris@epa.gov>

Date: 09/08/2017 05:21 PM

Subject: Re: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Hi Lidka,

Barbara (Glenn) and I are the current chemical managers of the formaldehyde assessment. We were hoping we might be able to set up a phone conversation to talk through the current status of the assessment and your questions below? If so, I can send out some type of Google poll or similar to find a time that works for everyone who might want to participate?

I would emphasize to you that the draft you mention was never finalized after it was released for the purposes of peer consultation and review. Thus, it should not be cited as an EPA position. We can explain this in greater detail when we talk.

We look forward to future conversations, Andrew and Barbara

From: Lidka Maslankiewicz < lidka.maslankiewicz@rivm.nl>

Sent: Tuesday, August 29, 2017 7:59 AM

To: Kraft, Andrew

Cc: Els Smit; Paul Janssen; Joke Herremans

Subject: Request for permission to use data from IRIS Toxicological Review of Formaldehyde (Inhalation)

Dear Dr Kraft,

My name is Lidka Maslankiewicz and I work at the Dutch National Institute for Public Health and the Environment (RIVM). We are currently busy with the update of the Maximum Permissible Risk (MPR) for formaldehyde.

We would like to use the approach and values described in IRIS Toxicological Review of Formaldehyde (Inhalation) (External Review Draft 2010), in particular Volume 3: "Quantitative Assessment, Major Conclusions in the Characterization of Hazard and Dose Response"

(<a href="https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614">https://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=223614</a>), to derive MPR value for the Netherlands. Could you, please, inform me, if this could be permitted? Are there more recent versions of this document? If we would be allowed to use your data, how we could refer to the source?



IRIS Toxicological Review of Formaldehyde (Inhalation ...
cfpub.epa.gov

EPA announces the release of the Toxicological Review of Formaldehyde-Inhalation Assessment in the June 2, 2010
Federal Register Notice. This draft assessment is ...

### IRIS Toxicological Review of Formaldehyde (Inhalation ...

cfpub.epa.gov

EPA announces the release of the Toxicological Review of Formaldehyde-Inhalation Assessment in the June 2, 2010 Federal Register Notice. This draft assessment is ...

Kind regards
Lidka
Lidka Maslankiewicz
National Institute for Public Health and the Environment (RIVM)
Centre for Safety of Substances and Products
tel. 31 (0)30 2743160
+31 6 46 86 07 73
fax. 31 (0)30 2744401

e-mail: Lidka.Maslankiewicz@rivm.nl

Dit bericht kan informatie bevatten die niet voor u is bestemd. Indien u niet de geadresseerde bent of dit bericht abusievelijk aan u is verzonden, wordt u verzocht dat aan de afzender te melden en het bericht te verwijderen. Het RIVM aanvaardt geen aansprakelijkheid voor schade, van welke aard ook, die verband houdt met risico's verbonden aan het elektronisch verzenden van berichten.

www.rivm.ni De zorg voor morgen begint vandaag

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| <u>www.rivm.nl</u> Dutch experts on climate change adaptation join forces. Fourteen Dutch |
| knowledge institutes have joined forces to provide practical, demand-driven               |
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| wetenschappelijke onderbouwing van het volksgezondheidsbeleid. Ook valt het<br>Informatiecentrum |

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| policy advice based                                                         |

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#### Message

From: Glenn, Barbara [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP

(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7A2DC9210D2D4D02A623B33F87F49436-GLENN, BARBARA]

**Sent**: 11/1/2017 4:39:55 PM

To: Bateson, Thomas [Bateson.Thomas@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Kraft, Andrew

[Kraft.Andrew@epa.gov]

**Subject**: RE: Formaldehyde Science Discussion

#### Ex. 5 - Deliberative Process

If you will

want to go over specific figures or tables that are in that section with Bruce, it would be a good idea to bring a copy of those to give him.

From: Bateson, Thomas

Sent: Wednesday, November 01, 2017 12:31 PM

To: Glenn, Barbara <Glenn.Barbara@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Kraft, Andrew

<Kraft.Andrew@epa.gov>

Subject: RE: Formaldehyde Science Discussion

Yes. I am going to bring those items. But wondering if Bruce is seeking additional reading, then might it save time to send the longer write-up for LHP.

From: Glenn, Barbara

Sent: Wednesday, November 01, 2017 12:28 PM

To: Bateson, Thomas <Bateson.Thomas@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Kraft, Andrew

<Kraft.Andrew@epa.gov>

**Subject:** RE: Formaldehyde Science Discussion

# Ex. 5 - Deliberative Process

Then we will discuss anything else Bruce would like.

-Barbara

From: Bateson, Thomas

Sent: Wednesday, November 01, 2017 11:53 AM

To: Thayer, Kris <thayer.kris@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Glenn, Barbara

<Glenn.Barbara@epa.gov>

Subject: RE: Formaldehyde Science Discussion

Consider if it might be useful to cut out the long form section on ML epi.



From: Thayer, Kris

Sent: Wednesday, November 01, 2017 11:51 AM

To: Kraft, Andrew < Kraft. Andrew@epa.gov>; Glenn, Barbara < Glenn. Barbara@epa.gov>; Bateson, Thomas

<Bateson.Thomas@epa.gov>

Subject: FW: Formaldehyde Science Discussion

I don't think we have any materials, correct

From: Sjogren, Mya

Sent: Wednesday, November 1, 2017 11:29 AM

To: Thayer, Kris <thayer.kris@epa.gov>

Cc: Fleming, Megan < Fleming. Megan@epa.gov > Subject: RE: Formaldehyde Science Discussion

Hi Kris,

Should we expect materials for this meeting? If so, when might they be available?

Thanks.

Mya Sjogren Immediate Office of the Assistant Administrator Office of Research and Development US EPA (202) 564-2213

-----Original Appointment-----

From: Rodan, Bruce

Sent: Wednesday, October 25, 2017 8:55 AM

To: Rodan, Bruce; Bahadori, Tina; Glenn, Barbara; Kraft, Andrew; Bateson, Thomas; Thayer, Kris; Sjogren, Mya; Fleming,

Megan

**Subject:** Formaldehyde Science Discussion

When: Thursday, November 02, 2017 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where: 41226 RRB/via video to Tina

Bruce asked for a science discussion with the IRIS formaldehyde assessment team early next week. Would you please arrange for this to include:

- Barbara Glenn
- Andrew Kraft
- Tom Bateson
- Kris Thayer

At first glance Tuesday 10/31/17 at noon looks good © on everyone's calendar. Hopefully we can snag that soon!!

Thanks,

Tina



| Message                     |                                                                                                                                                                                                                                                                                        |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| From: Sent: To: Subject:    | Glenn, Barbara [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7A2DC9210D2D4D02A623B33F87F49436-GLENN, BARBARA] 9/8/2017 4:30:42 PM Kraft, Andrew [Kraft.Andrew@epa.gov] RE: Program and Regional Patron or Client engagement on IRIS assessments |
| Subject.                    | RE. Flogram and Regional Fation of Cheft engagement of this assessments                                                                                                                                                                                                                |
| Thank you!                  |                                                                                                                                                                                                                                                                                        |
| From: Kraft                 |                                                                                                                                                                                                                                                                                        |
| -                           | 7, September 08, 2017 12:29 PM                                                                                                                                                                                                                                                         |
|                             | Barbara <glenn.barbara@epa.gov></glenn.barbara@epa.gov>                                                                                                                                                                                                                                |
| <b>Subject</b> : Re         | Program and Regional Patron or Client engagement on IRIS assessments                                                                                                                                                                                                                   |
| Looks good                  | to me. Thanks, Boss.                                                                                                                                                                                                                                                                   |
| From: Gleni<br>Sent: Friday | n, Barbara<br>r, September 8, 2017 12:26 PM                                                                                                                                                                                                                                            |
| To: Kraft, A                | ndrew                                                                                                                                                                                                                                                                                  |
| Subject: RE                 | Program and Regional Patron or Client engagement on IRIS assessments                                                                                                                                                                                                                   |
| Good?                       |                                                                                                                                                                                                                                                                                        |
|                             |                                                                                                                                                                                                                                                                                        |
| From: Kraft                 | , Andrew                                                                                                                                                                                                                                                                               |
| Sent: Friday                | , September 08, 2017 12:07 PM                                                                                                                                                                                                                                                          |
| To: Glenn, E                | Barbara < <u>Glenn.Barbara@epa.gov</u> >                                                                                                                                                                                                                                               |
| Subject: Re                 | Program and Regional Patron or Client engagement on IRIS assessments                                                                                                                                                                                                                   |

Found this, let's add:

High



|            |                                  | <br> | <br>     |   |              |   | , |                |
|------------|----------------------------------|------|----------|---|--------------|---|---|----------------|
| OAR        | Section 112(c) of the Clean Air  |      |          |   |              |   |   |                |
|            | Act section specifically lists   |      |          |   |              |   |   |                |
|            | formaldehyde as a "hazardous     |      |          |   |              |   |   |                |
|            | air pollutant". Section 112(d)   |      |          |   |              |   |   |                |
|            | requires national emissions      |      |          |   |              |   |   |                |
|            | standards for industrial         |      |          |   | -            |   |   |                |
|            | sources of                       |      |          |   |              |   |   |                |
|            | formaldehyde. Section 202(I)     |      |          |   |              |   |   |                |
|            | requires control of mobile       |      |          |   |              |   |   |                |
|            | sources of formaldehyde and      |      |          |   |              |   |   |                |
|            | other hazardous air              |      |          |   |              |   |   |                |
|            | pollutants. OAR has multiple     |      |          |   |              |   |   |                |
|            | source categories for which      |      |          |   |              |   |   |                |
|            | regulatory decisions using       |      |          |   |              |   |   |                |
|            | formaldehyde toxicity values     |      |          |   |              |   |   |                |
|            | need to be addressed.            |      |          |   |              |   |   |                |
| OW         |                                  |      |          |   |              |   |   |                |
| OW         | Section 311(b)(2)(A) of the      |      |          |   |              |   |   |                |
|            | Clean Water Act requires OW      |      |          |   |              |   |   |                |
|            | to regulate discharges of        |      |          |   | 7            |   |   |                |
|            | hazardous substances, duch as    |      |          |   |              |   |   |                |
|            | formaldehyde. CWA also           |      |          |   |              |   |   |                |
|            | requires EPA to set reportable   |      |          |   |              |   |   |                |
|            | quantities for hazardous         |      |          |   |              |   |   |                |
|            | substances, such as              |      |          |   |              |   |   |                |
|            | formaldehyde [rules at 40 CFR    |      |          |   |              |   |   |                |
|            | 117]. Formaldehyde is listed in  |      |          |   |              |   |   |                |
|            | EPA regulations as a hazardous   |      | T        |   | Tue u eue it |   |   | [Tue 10 aug.:4 |
|            | substance under the              |      | Transmit |   | Transmit     |   |   | [Transmit      |
|            | CWA. States also make            |      | for      |   | for          |   |   | for Public     |
|            | decisions for which              |      | intra-   |   | Inter-       |   |   | Comment in     |
|            | formaldehyde toxicity would      |      | agency   |   | agency       |   |   | January        |
|            | be a consideration.              |      | review   |   | Review       |   |   | 2018]          |
| Medium     |                                  |      |          |   | 7            |   |   |                |
| OPPT/OCSPP | Title VI of the Toxic Substances |      |          |   |              |   |   |                |
| ,          | Control Act (TSCA) requires      |      |          |   |              |   |   |                |
|            | EPA to regulate formaldehyde     |      |          |   |              |   |   |                |
|            | emissions from composite         |      |          |   |              |   |   |                |
|            | wood products. TSCA              |      |          |   |              |   |   |                |
|            | regulates significant new uses   |      |          |   |              |   |   |                |
|            | of formaldehyde pursuant to      |      |          |   |              |   |   |                |
|            | Section 5(a)(2) of TSCA. The     |      |          |   |              |   |   |                |
|            | Toxic Substances Control Act     |      |          |   |              |   |   |                |
|            | <b>}</b>                         |      |          |   | -            |   |   |                |
|            | (TSCA) gives EPA authority to    |      |          |   |              |   |   |                |
|            | regulate chemical substances     |      |          |   |              |   |   |                |
|            | and/or mixtures;                 |      |          |   | 7            |   |   |                |
|            | formaldehyde was added to        |      |          |   |              |   |   |                |
|            | the OPPT Work Plan for           |      |          |   |              |   |   |                |
|            | Chemical Assessments in 2012.    |      |          |   |              |   |   |                |
| OPP/OCSPP  | FIFRA requires EPA to make       |      |          |   |              |   |   |                |
|            | registration and labeling        |      |          |   | 7            |   |   |                |
|            | decisions on                     |      |          |   |              |   |   |                |
|            | antimicrobials. Manufacturers    |      |          |   | 7            |   |   |                |
|            | of a range of products have      |      |          |   |              |   |   |                |
|            | identified formaldehyde as an    |      |          |   |              |   |   |                |
|            | ingredient having antimicrobial  |      |          |   |              |   |   |                |
|            | properties and thus subject to   |      |          |   |              |   |   |                |
|            | FIFRA authority. States can      |      |          |   |              |   |   |                |
|            | sometimes have parallel or       |      |          |   |              |   |   |                |
|            |                                  |      |          | ı | Į.           | ı | i | ,              |

|          | supplemental requirements<br>where allowed under FIFRA<br>Section 24(a).                                                                                                                                                                                                                                                                                                          |  |  |  |  |  |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|--|
| Other    |                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |  |  |
| OLEM     | RCRA regulations classify as hazardous wastes discarded commercial products and other wastes containing formaldehyde 940 CFR 261.33) and RCRA requires EPA to regulate the storage, treatment and disposal of hazardous wastes. Formaldehyde is a hazardous substance and contaminated sites containing formaldehyde can be subject to clean-up authorities under CERCLA or RCRA. |  |  |  |  |  |
| Region 5 |                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |  |  |
| OA-OCHP  | Significant interest in formaldehyde association with asthma.                                                                                                                                                                                                                                                                                                                     |  |  |  |  |  |

From: Glenn, Barbara

Sent: Friday, September 8, 2017 11:52 AM

To: Glenn, Barbara; Kraft, Andrew

Subject: FW: Program and Regional Patron or Client engagement on IRIS assessments

From: Kraft, Andrew

**Sent:** Friday, September 08, 2017 11:41 AM **To:** Glenn, Barbara < Glenn.Barbara@epa.gov >

Subject: Re: Program and Regional Patron or Client engagement on IRIS assessments



The interactions with OCSPP were within the last 12 months, as well, so we can probably add them. For air, I would just note that it is their 1st, 2nd, and 3rd need when NCEA reached out last winter

From: Glenn, Barbara

Sent: Friday, September 8, 2017 8:17 AM

To: Kraft, Andrew Does this look OK?

Subject: RE: Program and Regional Patron or Client engagement on IRIS assessments

Patrons/clients:

Office of Air: had a meeting to find out their priorities and needs re: formaldehyde 2 years ago (can't remember who was there)

OPP: conducting a microbials rule; Meetings and communications several times this year (approx. 5 interactions) – Timothy Leighton and Timothy Dole of OPP

OCSPP – interactions during the year regarding the wood rule

Interactions with RAD (in OPPT) on an azo dye releaser last winter

Regions: Region 5 asked about the status of the formaldehyde assessment for discussion with State partners at a Regional/State meeting; Rae Trine, Air toxic and assessment branch in Region 5 – Phone conversation in August 2017

From: Kraft, Andrew

**Sent:** Thursday, September 07, 2017 2:54 PM **To:** Glenn, Barbara < Glenn.Barbara@epa.gov>

Subject: FW: Program and Regional Patron or Client engagement on IRIS assessments

I suppose we need to do this too...

From: Lavoie, Emma

Sent: Monday, August 28, 2017 10:03 AM

To: Davis, Allen < Davis. Allen@epa.gov>; Lee, Janice < Lee. Janice S@epa.gov>; Gibbons, Catherine

<<u>Gibbons.Catherine@epa.gov</u>>; Sasso, Alan <<u>Sasso.Alan@epa.gov</u>>; Arzuaga, Xabier <<u>Arzuaga.Xabier@epa.gov</u>>;

Weaver, Andre < Weaver.James@epa.gov>; Yost, Erin < Yost. Erin@epa.gov>; Keshava, Nagalakshmi

<Keshava.Nagu@epa.gov>; Glenn, Barbara <Glenn.Barbara@epa.gov>; Kraft, Andrew <Kraft.Andrew@epa.gov>; Segal,

Deborah <Segal Deborah@epa.gov>; Keshava, Channa <Keshava.Channa@epa.gov>; Druwe, Ingrid



<<u>Druwe.ingrid@epa.gov</u>>; Li, Jenny <<u>Li.Jenny@epa.gov</u>>; Pardo, Larissa <<u>Pardo.Larissa@epa.gov</u>>; Hogan, Karen <<u>Hogan.Karen@epa.gov</u>>; Pratt, Margaret <<u>pratt.margaret@epa.gov</u>>; Carlson, Laura <<u>Carlson.Laura@epa.gov</u>>; Lehmann, Geniece <<u>Lehmann.Geniece@epa.gov</u>>

**Cc:** Thayer, Kris < <a href="mailto:thayer.kris@epa.gov">thayer.kris@epa.gov">thayer.kris@epa.gov</a>; Avery, James <a href="mailto:Avery.James@epa.gov">Avery.James@epa.gov</a>; Fritz, Jason <a href="mailto:Fritz.Jason@epa.gov">Fritz.Jason@epa.gov</a>; Soto, Vicki <a href="mailto:Vicki@epa.gov">Soto, Vicki@epa.gov</a>>

Subject: Program and Regional Patron or Client engagement on IRIS assessments

IRIS assessment managers:

I'd like to check-in with you about who and how often you are engaging your clients/partners/patrons in the program and regional offices.

Please reply to me with the following information (briefly):

Who do you consider your 'patron' or 'client' in the Programs and/or Regions?

How often do you interact with them e.g., give updates, answer questions or give presentations? How often in the last 12 months?

I'll use this information to work with you to improve or refine our interactions as assessments move forward.

I have worked with some of you in the last year on Patron/client interactions but may not have discussed this much in the last few months. If an assessment manager is missing from this email, it is because I have recent activity with them regarding their Patrons or their assessment is in SAB review.

For phthalates, Erin Yost has started this conversation with me, but if you have anything specific on any part of the phthalates work, please still share it.

Otherwise I'm specifically interested in these assessments:

Arsenic inorg

**BBP** 

Chromium VI

DBP

DEP

DIBP

DINP

Formaldehyde

Naphthalene



Nitrate Nitrite PAH RPFs PCBs tert-Butanol

-Emma

Emma T. Lavoie, PhD

Assistant Center Director for Scientific Support

National Center for Environmental Assessment US Environmental Protection Agency

Tel: 703-347-0328

